OCT 9 1943

Medical Library

VOLUME 47 NUMBER 3

ARCHIVES OF SURGERY

EDITORIAL BOARD

CAPTAIN WALTMAN WALTERS, MC-V(S),U.S.N.R., Chairman
LESTER R. DRAGSTEDT, Chairman Pro Tem, Chicago
EVARTS A. GRAHAM, St. Louis
ALFRED BLALOCK, Baltimore
ALTON OCHSNER, New Orleans
A. J. SCHOLL, Los Angeles
ARTHUR W. ALLEN, Boston
WILLIAM DARRACH, New York
WALTER E. DANDY, Baltimore

SEPTEMBER 1943

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter July 10, 1925, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

COPYRIGHT, 1943, BY THE AMERICAN MEDICAL ASSOCIATION

CONTENTS OF PREVIOUS NUMBER

AUGUST 1943. NUMBER 2

Pathologic Study of Degeneration and Rupture of the Supraspinatus Tendon. C. Laird Wilson, M.D., C.M., and G. Lyman Duff, M.D., Ph.D., Montreal, Canada.

Anatomic and Clinical Study of the Transverse Abdominal Incision. Vincent L. Rees, M.D., and Frederick A. Coller, M.D., Ann Arbor, Mich.

Primary Intracranial Lymphosarcoma: A Report of Two Cases and Review of the Literature. Kenneth H. Abbott, M.D., and Alfred W. Adson, M.D., Rochester, Minn.

Effect of Division of the Sphincter of Oddi on the Bile Diastase of the Dog. S. H. Gray, M.D.; Carl J. Heifetz, M.D., and J. G. Probstein, M.D., with the Technical Assistance of Simon Russi, M.D., St. Louis.

Unusual Cases of Hyperinsulinism and Hypoglycemia. Commander Emile Holman (MC), U.S.N.R., and David A. Wood, M.D., and Andrew B. Stockton, M.D., San Francisco.

Hemorrhagic Hypotension and Its Treatment by Intra-Arterial and Intravenous Infusion of Blood. K. G. Kohlstaedt, M.D., and Irvine H. Page, M.D., Indianapolis.

Bilateral Carcinoma of the Adrenal Cortex with Metastasis to Iliac Bone. Mather Cleveland, M.D., and Leila Charlton Knox, M.D., New York.

Confinement to Bed for Only Twenty-Four Hours After Operation: A Means of Preventing Pulmonary and Circulatory Complications and of Shortening the Period of Convalescence. D. J. Leithauser, M.D., Detroit.

The Ceiling of Utilization of Nitrogen: Effect of Continuous Venoclysis with the Amino Acids of Hydrolyzed Protein During Experimental Hypoalbuminemia. Robert Elman, M.D.; Ray Charnas, M.D., and Harriet W. Davey, B.A., St. Louis.

ARCHIVES OF SURGERY

VOLUME 47 SEPTEMBER 1943 NUMBER 3

COPYRIGHT, 1943, BY THE AMERICAN MEDICAL ASSOCIATION

CARCINOID TUMORS (SO-CALLED) OF THE ILEUM

REPORT OF THIRTEEN CASES IN WHICH THERE WAS METASTASIS

MALCOLM B. DOCKERTY, M.D.*
AND
FRANK S. ASHBURN, M.D.
Fellow in Surgery, Mayo Foundation
ROCHESTER, MINN.

Carcinoid tumors are rare, but, judging from the volume of literature concerning them, probably few lesions of equal obscurity have received the same degree of attention. Moreover, the relatively common appendical carcinoid tumor has been superseded in point of interest by a small group localized elsewhere in the gastrointestinal tract, notably in the ileum. There are many reasons why this small group has merited what many believe to be unwarranted attention. Whereas appendical carcinoid tumors are often symptomless, those involving the ileum produce clinical evidence of obstruction in about one third of the cases, and small tumors thus located may produce major disturbances. Appendical carcinoid tumors are usually single, whereas about 25 per cent of their ileal counterparts appear as multiple tumor nodules.

But perhaps the most interesting feature connected with the group as a whole concerns the question of malignancy. Carcinoid tumors were regarded originally as ordinary (although small)[1] carcinomas, but the investigations of Oberndorfer[2] emphasized their essentially benign character, and the term "carcinoid" was coined to express the paradox of their malignant appearance contrasting with their benign clinical course. This view prevailed for a number of years, in spite of early (Ranson, 1890)[3] evidence that metastasis occasionally takes place. Carcinoids then became "debatable tumors," with investigators contributing cases singly or in small groups. Many histogenic studies were attempted, and although no less than thirteen hypotheses of origin [4] have been listed as "current possibilities," the majority of contributors felt with Masson [5] that the tumors arise through a proliferation of chromoargentaffin cells native to the crypts of Lieberkühn. In the present paper no attempt will be made to detail the evolution of knowledge concerning carcinoids.

* Division of Surgical Pathology, Mayo Clinic.

1. Lubarsch, O.: Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberkulose, Virchows Arch. f. path. Anat. **111**:280-317, 1888.

2. Oberndorfer, S.: Karzinoide Tumoren des Dünndarms, Frankfurt. Ztschr. f. Path. **1**: 426-432, 1907.

3. Ranson, W. B.: Primary Carcinoma of the Ileum, Lancet **2**:1020, 1890.

4. Collins, D. C.; Collins, F. K., and Andrews, V. L.: Ulcerating Carcinoid Tumor of Meckel's Diverticulum, Am. J. Surg. **40**:454-461 (May) 1938.

5. Masson, P.: Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, Am. J. Path. **4**:181-213 (May) 1928.

For this information the reader is referred to numerous excellent reviews.[6] Our prime concern is an inquiry into the malignant propensities of these tumors—a fact still debated if not actually doubted by many.[7]

MATERIALS AND METHODS

Records from the Division of Surgical Pathology and the Section on Pathologic Anatomy of the Mayo Clinic were searched for cases in which the diagnosis was carcinoma, adenocarcinoma, carcinoid, argentaffin tumor, and so forth, involving the small intestine. Pathologic material from some 130 cases of such growths had been seen at the clinic between the years 1906 and 1943. This material was next obtained and studied in conjunction with clinical records in a weeding-out process designed to eliminate metastatic tumors from the series. Material from all "primary" growths was next studied, and sections were taken and examined by the rapid freezing technic, polychrome methylene blue being used as a stain. This procedure readily eliminated all but the obvious carcinoids and a small group of neoplasms which we labeled as doubtful until they were later accepted as examples of carcinoid tumors or rejected, on the basis of permanent hematoxylin and eosin preparations. The residual group of 30 specimens was then reassembled and reviewed in gross detail with special attention to the following features: the location of the tumor in relation to the ileocecal valve, and when possible to the mesenteric attachment; the size, shape, color, consistency and mode of origin (whether unicentric or multicentric) of the tumors; the mucosal relation, whether ulcerated or nonulcerated, together with any tendency toward intussusception; the condition of the muscularis and peritoneum with special reference to infiltration, "buckling," myohypertrophy, obstruction and so forth; the condition of the mesentery in relation to invasion, the presence or absence of involved lymph nodes and the mode of such involvement, whether by direct extension, by lymphatic permeation or by the embolic route. These and other pertinent data were recorded carefully for the purposes of analysis. Multiple blocks of tissue were then cut from the tumors. These were selected so as to include the junction of the mucosa with the tumor, the growing edge of the tumor, the peritoneal surfaces overlying and adjacent to the tumor and the adjacent mesentery with the involved and the uninvolved lymph nodes. In addition, sections were taken from the mucosa of the ileum proximal and distal to the growths, and from the appendix and the colon when available. All of these blocks were placed in a fresh 4 per cent solution of formaldehyde. They were sectioned at a thickness of 10 microns on a freezing microtome and stained routinely with hematoxylin and eosin. Residual portions of these blocks were prepared subsequently by the paraffin technic and were stained by the Galantha method for mucus. In addition, Becker's and Bielschowsky's methods were employed to demonstrate the specific argentaffin granules. In all, some 200 slides were made available for study.

---

6. (*a*) Ariel, I. M.: Argentaffin (Carcinoid) Tumors of the Small Intestine: Report of Eleven Cases and Review of the Literature, Arch. Path. **27**:25-52 (Jan.) 1939. (*b*) Cooke, H. H.: Carcinoid Tumors of Small Intestine, Arch. Surg. **22**:568-597 (April) 1931. (*c*) Forbus, W. D.: Argentaffine Tumors of the Appendix and Small Intestine, Bull. Johns Hopkins Hosp. **37**:130-153 (Aug.) 1925. (*d*) Gáspár, I.: Metastasizing "Carcinoid" Tumor of Jejunum, Am. J. Path. **6**:515-524 (Sept.) 1930. (*e*) Porter, J., and Whelan, C.: Argentaffine Tumors: Report of Eighty-Four Cases, Three with Metastasis, Am. J. Cancer **36**: 343-358 (July) 1939. (*f*) Raiford, T. S.: Carcinoid Tumors of the Gastro-Intestinal Tract (So-Called Argentaffine Tumors), ibid. **18**:803-833 (Aug.) 1933. (*g*) Wyatt, T. E.: Argentaffine Tumors of the Gastro-Intestinal Tract: Report of Three Cases, One with Distant Metastases, Ann. Surg. **107**:260-269 (Feb.) 1938. (*h*) Masson.[5]

7. Cohn, S.; Landy, J. A., and Richter, M.: Tumors of the Small Intestine, Arch. Surg. **39**:647-660 (Oct.) 1939.

The central theme of this presentation concerns 13 of the 30 cases in which undoubted evidence of metastasis was found by the method outlined previously. Many of these lesions were not clinically silent. We believe, therefore, that the recording and the correlation, when possible, of clinical details with pathologic findings are necessary for a proper understanding of carcinoid tumors. In addition, it is hoped that the presentation of such a large series will open up new channels of investigation directed toward solving the problem of early diagnosis of carcinoid tumors, a problem which so far has not seen any satisfactory solution.

REPORT OF CASES

CASE 1 (Previously reported briefly [7a]).—A man aged 42 years came to the Mayo Clinic Aug. 7, 1940, because of five years of abdominal discomfort. His medical history was irrelevant. The illness of which he complained had taken the form of attacks of epigastric distress. Although pain was not an early complaint, the distress bore some of the clinical hallmarks of ulcer in that it was more or less periodic, came on about two hours after meals, lasted a variable time and then disappeared gradually. No nausea or vomiting had been noted, and "night pain" had not been experienced. During one of the episodes the distress amounted to a severe pain requiring morphine for relief. Operation had been advised but had been refused by the patient, who had been "carried over" on a medical regimen supplemented with "injections." Mild diarrhea had developed about two years after the onset of the trouble, and simultaneously the patient began to experience some distress in the lower portion of the abdomen. This distress, occasionally complicated by actual colicky pain, also came on soon after the ingestion of food and was accompanied by belching, flatulence, a feeling of fulness and an increase of the severity of the diarrhea. Occasional slight melena had been noted by the patient and had been attributed to hemorrhoids. Relief of symptoms by the use of special diets had been tried, but with no success, and the patient, who had been gradually lowering his intake of food in order to avoid abdominal discomfort, had lost weight progressively.

Essential positive findings on examination were limited to the observations of mild wasting, slight exophthalmos (unilateral and congenital), internal hemorrhoids and a firm, movable, nontender mass located in the left hypochondrium. The mass was estimated to measure 8 cm. in diameter and was believed to be a mesenteric cyst.

Results of hematologic examination and analysis of gastric contents were normal. Urinalysis revealed mild albuminuria with pyuria. Results of roentgenologic examination of the stomach and colon were interpreted as not revealing any intrinsic abnormalities. The presence of small bilateral renal calculi (clinically silent) was demonstrated on roentgenograms of the kidneys, but it was ascertained on the basis of further urologic investigation that renal function was good.

Exploratory laparotomy was performed through a low midline incision on Sept. 16, 1940. At operation multiple tumors of varying size, involving the ileum and its mesentery, the regional nodes and the parietal peritoneum were observed. In addition, small masses, obviously metastatic, were felt in the right and the left lobe of the liver. Several of the smaller nodules from the mesentery were removed for biopsy and were reported as carcinoid tumors on the basis of frozen sections, the polychrome technic of rapid staining being used. Accordingly 52 inches (132 cm.) of the terminal portion of the ileum was resected in a procedure designed to include all of the intrinsic tumor nodules and the regional nodes. The severed ends of the ileum were next closed and gastrointestinal continuity was reestablished by means of side to side ileoileostomy. On examination the appendix was ascertained to be normal and was not disturbed. Postoperatively a transfusion of whole blood was administered. The patient was dismissed fifteen days after operation, and when he returned for hemorrhoidectomy eighteen months later there was little evidence of deterioration of his condition. He was living and well when last heard from, twenty-eight months after his first admission.

Pathologic Data.—The surgical specimen consisted of 52 inches (132 cm.) of ileum, extending upward from a resection level some 10 inches (25 cm.) proximal to the ileocecal valve, and several small nodules of tissue removed from the pelvic peritoneum. Scattered throughout the resected segment were sixty-eight isolated orange-yellow nodules varying in diameter from 3.5 cm. to 2 mm. (fig. 1). These nodules were not by any means limited to, or even concen-

7a. Pennington, R. E., and Priestley, J. I.: Multiple Carcinoid Tumors of Small Intestine: Report of Case, Proc. Staff Meet., Mayo Clin. **18**:49-51 (Feb. 24) 1943.

trated on, the antimesenteric border. (Such a localization has been discussed in the literature.[8]) All appeared to be covered at least in part by the mucosa of the intestine. In the case of the larger nodules some very superficial erosion of the mucosa was apparent and there was outcropping of the underlying yellowish tumor tissue. These "raw surfaces" presented very little in the way of inflammatory reactions. In other words, the typical appearance of deep ulcers with necrotic bases was lacking, in sharp contrast to the picture seen in ordinary carcinoma of the ileum. With smaller lesions a deeper location seemed indicated. Some of the latter were present within the apexes of the transverse mucosal folds, whereas others lay more or less concealed in the intervening grooves. Several of the larger lesions, although relatively small, appeared to be producing obstruction by virtue of intussusception in addition to an observed tendency toward narrowing of the lumen through fibrous contraction. Proximal to these semi-obstructed zones the lumen of the ileum was dilated, the mucosa thrown into heavy corrugated folds pitted with superficial erosions and the muscularis considerably hypertrophied.

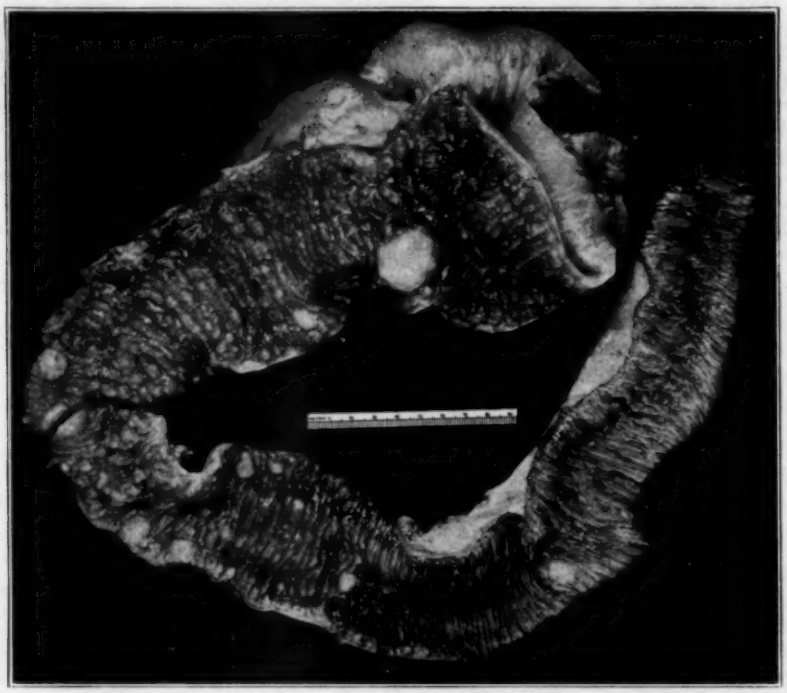

Fig. 1 (case 1).—Surgical specimen containing sixty-eight independent grade 1 adenocarcinomas (carcinoid type).

The peritoneum overlying several of the larger nodules was puckered and indurated in an obvious process of malignant infiltration. Smaller nodules did not demonstrate this form of extension, since they were grossly limited to the mucosa and submucosa. Mesenteric nodes were manifestly involved in several regions related to the larger lesions described previously. Primary and metastatic nodules, including those removed for biopsy from the pelvis, demonstrated the peculiar orange-yellow color so typical of carcinoid tumor.

Sixty centimeters from the lower end of the resected loop a Meckel diverticulum 2.5 by 2 by 2 cm. was found located, as is usual, on the antimesenteric surface of the ileum. It did not contain any tumor nodules. Likewise none was present in the proximal 25 cm. and the distal 8 cm. of the resected segment of ileum.

Microscopically, all of the tumors were typically carcinoid, and individually as well as in groups they duplicated practically all of the variations depicted in the literature on these tumors. Accordingly no useful purpose would be served by repeating a detailed description of all the histologic patterns encountered. On the other hand, the opportunity of studying so many

8. Pack, G. T., and Davis, A. H.: Carcinoid Tumors of the Small Intestine, Am. J. Surg. **9**:472-477 (Sept.) 1930.

tumors, in various stages of evolution and occurring simultaneously in the same segment of ileum, brought out many features not to be observed in other cases. The following observations therefore deal primarily with these features.

1. Mucosa: In the case of the larger tumors superficial ulceration was present and in a few areas a thin layer of inflammatory granulation tissue covered the superficial aspects of the tumor. The ulcerations, however, could be termed little more than erosions and usually were located over the convexity of the underlying neoplasm (fig. 2*a*). More peripherally a submucosal infiltration was apparent with an elevation and stretching out of the crypts of Lieberkühn. The lack of deep ulceration was interpreted, after a study of the slides, as depend-

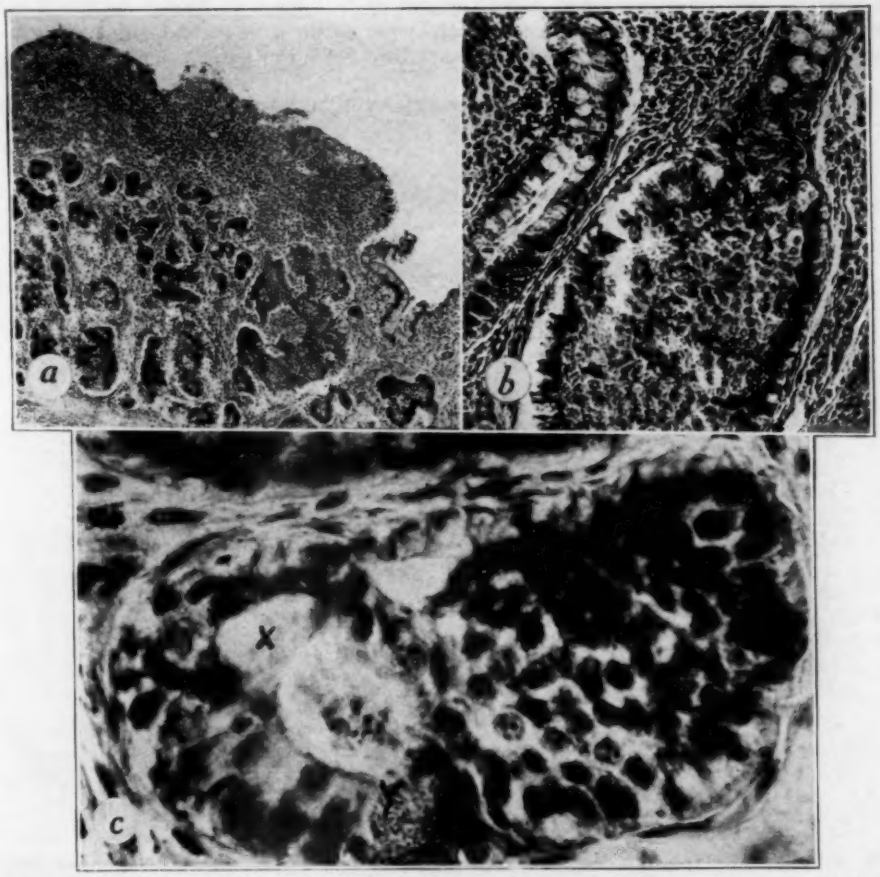

Fig. 2 (case 1).—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin): (*a*) superficial ulceration; the mucosa of the ileum is seen at the upper extremity; note the characteristic appearance of small, uniform, darkly staining tumor cells arranged in islands and cords (× 50); (*b*) point of origin in base of a crypt of Lieberkühn; tumor cells palisaded peripherally; a group of granular (Paneth and Kultschitzky) cells are seen lining an adjacent crypt (× 200); (*c*) origin of a tumor from a crypt in which mucous (*X*) and Paneth (*Y*) cells are still identifiable; note the uniformly small size of the tumor cells and the punctate basophilic granularity of their nuclei (× 620).

ing on three prime factors which seemed to be in operation in all of the tumors examined: (1) an extreme degree of fibrosis between the islands of tumor tissue, (2) a strange lack of the necrosis so commonly observed in other forms of gastrointestinal malignant lesions and (3) a notable lack of vascularity. With some of the small tumor nodules the aforementioned erosion of the mucosa was minimal and occasionally absent.

Several of the nodules were small enough to demonstrate that a considerable portion of tumorous tissue lay superficial to the muscularis mucosae. In two of these, fortuitous sections actually demonstrated the histogenesis of the tumor cells through a process of budding from

the granular elements located deeply in a crypt of Lieberkühn (fig. 2 *b* and *c*). This finding substantiated the view that carcinoid tumors actually begin in the mucosa. Further support of this view was afforded by the observation that these small tumors, freed as they were from the effects of reactive fibrosis so prominent in larger lesions, presented beautiful evidence of formation of glands. Moreover, it was observed that (fig. 3 *a* and *b*) many of these glands assumed oval or elongated rather than rounded forms. (This finding was noteworthy, because it refutes the claim [9] that the rounded "pseudo-acini" of carcinoids are rosettes and therefore probably of neuroectodermal rather than entodermal origin.) In many instances it was almost impossible to distinguish between the acinus-like groups of tumor cells and the "artefactitious" acini of the overlying crypts brought out by oblique sections; both contained granular cells and both gave evidence of secretion in that their lumens contained deposits. It was observed, however, that whereas mitotic figures were common in the cells lining the crypts, they were rarely observed in the groups of tumor acini. (When mitotic figures were observed

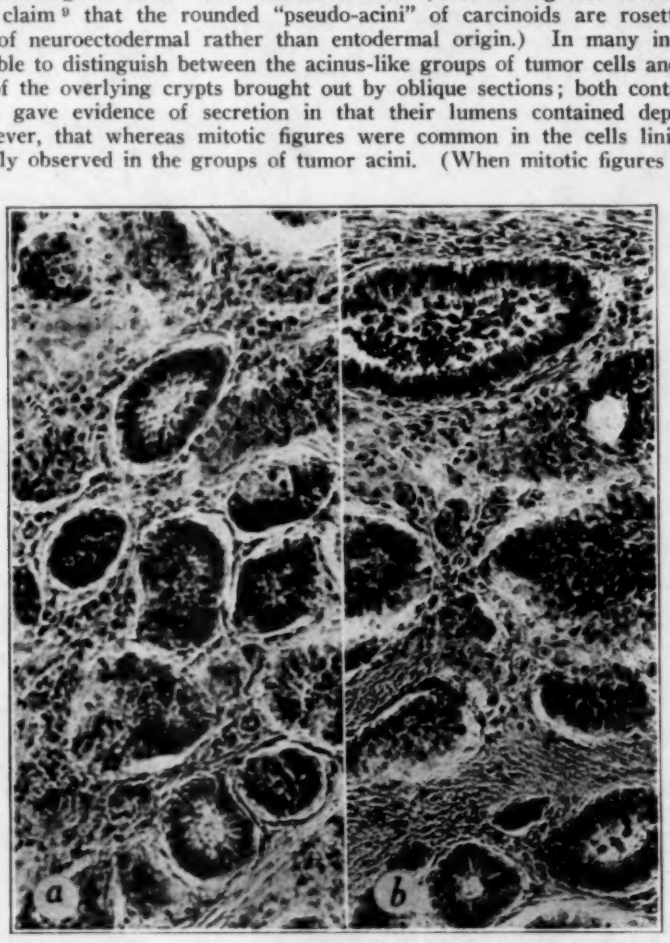

Fig. 3 (case 1).—Grade 1 adenocarcinoma (carcinoid). The illustration shows angular and oval tumor acini in addition to the rounded type (so-called rosettes of early writers). The stroma is only moderately fibrotic and certainly not vascular. (Hematoxylin and eosin; × 200.)

there it was practically always in small mucosal tumors.) The aforementioned tumor acini, which were studied in careful detail and compared cytologically with the parent cells in the overlying mucosa, appeared to be differentiated to a large degree. This observation obtained also in a study of the larger (metastasizing) nodules.

It therefore became apparent (1) that the tumor cells arose from and produced true glandular spaces—hence that the neoplasms were true adenocarcinomas and (2) that considerable differentiation, histologically and cytologically, was present in the smaller tumors, and cytologically even in those in which the microscopic picture was modified by secondary changes, such as fibrosis. Accordingly the designation grade 1 adenocarcinoma (carcinoid) seemed applicable to each of the several nodules.

9. Lewis, D., and Geschickter, C. F.: Tumors of the Sympathetic Nervous System (Neuroblastoma, Paraganglioma and Ganglioneuroma), Arch. Surg. **28**:16-58 (Jan.) 1934.

The muscularis mucosae always presented evidence of invasion, and in the majority of instances most of the tumorous tissue was situated outside rather than inside this layer. This observation is natural if one realizes that the point of origin of carcinoid is primarily the bases of the crypts which lie adjacent to the muscularis mucosae. Invasion of this layer appeared to result in thickening and fibrosis of a degree not observed in carcinoid cells invading the stroma of the mucosal glands. Along with the fibrosis there appeared to be a compression of the tumor cells, which no longer showed the numbers of typical acini described previously but rather had a tendency to grouping in strands and islands.

2. Submucosa and Muscularis: In the submucosa the groups of tumor cells again appeared in nests, islands or strands not presenting any unusual characteristics except a tendency to invade lymphatic spaces, especially those which were perineural. In the muscularis propria two features deserve mention: (1) considerable myohypertrophy associated with (or perhaps followed by) fibrosis and (2) invasion of the lymphatic spaces between the muscle bundles by tumor cells.

3. Peritoneum and Mesentery: Fibrosis was pronounced wherever the tumor cells were found and probably explained the "stenosis" of the intestine observed even with relatively small

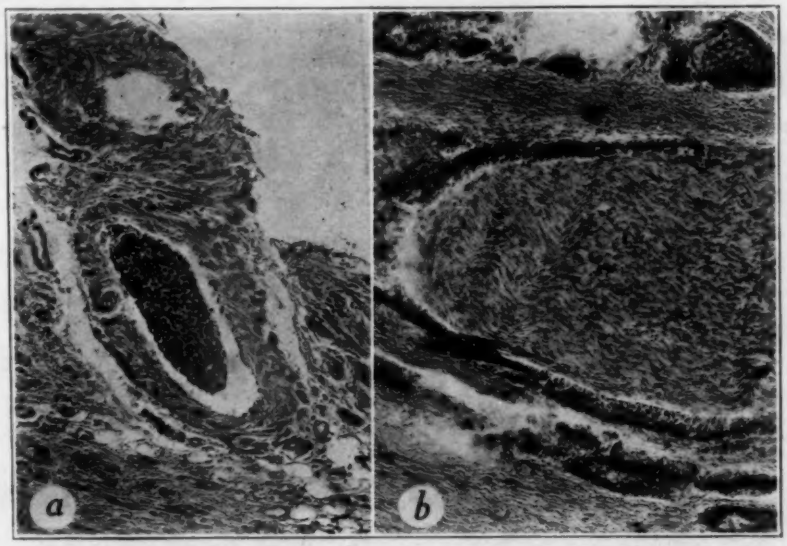

Fig. 4 (case 1).—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin × 100): (*a*) tumor thrombus within the lumen of a vein; (*b*) invasion by tumor cells of the perineural lymphatic spaces. The nerve is hypertrophied but is by no means a neuroma.

carcinoid tumors. Extension of a tumor was characterized by four features: (1) direct extension, (2) invasion of blood vessels (fig. 4 *a*), (3) invasion of ordinary lymphatic spaces and (4) a strong tendency to invade the perineural lymphatic spaces (fig. 4 *b*). The nerves appeared to be hypertrophied, but whether as a result of work hypertrophy (obstruction of intestine) or of direct irritation could not be ascertained. There was no evidence of formation of neuroma.

4. Regional Nodes: Regional nodes were involved rather extensively by tumor, and in several instances the mode of spread was admittedly by direct extension. However, in other nodes located at some distance from the growth, embolic phenomena were present, with typical early carcinomatous invasion of the peripheral sinuses (fig. 5 *a*). This we regarded as an important observation, refuting the view that the spread of carcinoid tumors does not represent true metastasis. Focal fibrosis of some degree was present in some regions, recalling the appearance of scirrhous carcinoma (fig. 5 *b*). Other histologic features worthy of mention were the subacutely inflamed condition of the villous folds proximal to the major regions of tumor involvement and the presence of numerous acidophilic (Paneth [10]-Kultschitzky [11])

10. Paneth, J.: Ueber die secernirenden Zellen des Dünndarm-Epithels, Arch. f. mikr. Anat. **31**:113-191, 1888.

11. Kultschitzky, N.: Zur Frage über den Bau des Darmkanals, Arch. f. mikr. Anat. **49**:7-35, 1897.

cells in the mucosa of almost every specimen examined. Staining methods employing the principle of silver impregnation demonstrated that these cells contained granular elements similar to those of the cells of the tumor. However, lipid-containing vacuoles observed in the cytoplasm of the carcinoid cells did not have any counterpart in the mucosa as demonstrated by the sudan III method. Results of study by serial sections of grossly normal mucosa between adjacent tumor nodules indicated a multicentric mode of origin rather than spread from a single primary focus.

CASE 2.—A white man aged 78 first registered at the clinic on Feb. 19, 1941, complaining of "gas on the stomach" of four months' duration. Inquiry revealed that the patient's mother and one of his brothers had died of carcinoma of the stomach. The patient had been well previously except for an attack of appendicitis in 1930, which had been treated successfully by appendectomy.

The illness of which he complained had taken the form of abdominal distention and belching, gradual in onset, but complicated on three occasions by episodes suggesting intestinal obstruction. On each occasion hospitalization and treatment with "nasal suction" had been necessary. The last of these three attacks had begun three days prior to admission and had persisted with some recent abatement.

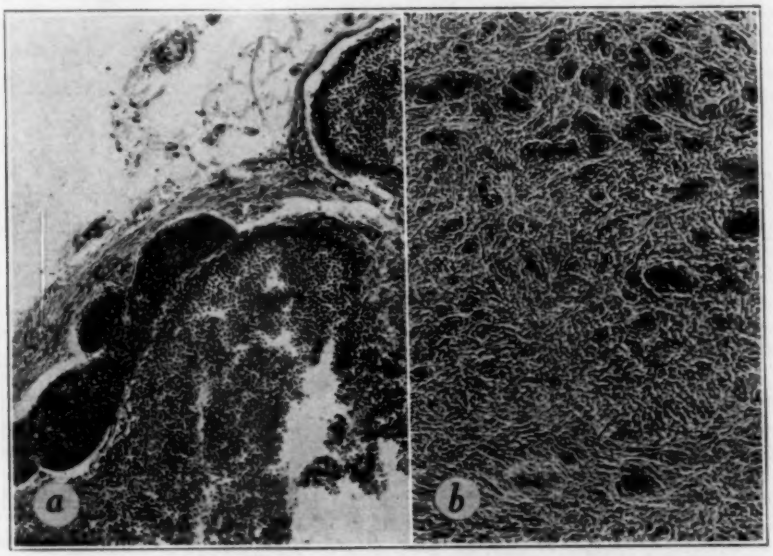

Fig. 5 (case 1).—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin): (*a*) "carcinoid" cells apparently still limited to the peripheral sinus of a lymphatic node (× 70); (*b*) fibrosis about the tumor cells in this node recalls the picture of scirrhous carcinoma (× 100).

Examination disclosed an undernourished, obviously dehydrated white man whose abdomen was moderately distended and tympanitic. Borborygmus was present and peristalsis was easily visible through a thin abdominal wall. No masses were palpable in the abdomen. Rectal examination disclosed what was interpreted clinically as benign prostatic hypertrophy, grade 3 (on the basis of 1 to 4). After a three day period of observation in which medical treatment succeeded in relieving in large degree the clinical signs of intestinal obstruction, proctoscopic and roentgenologic investigations of the rectum and colon were carried out. In the latter examination it was ascertained that the cecum was deformed by an extrinsic lesion which was interpreted as probably originating in the terminal portion of the ileum. Results of other laboratory examinations were essentially normal.

Inasmuch as the clinical history pointed rather strongly to the obstructive nature of the lesion, it was judged unwise to attempt further localization by means of roentgenologic examination of the small intestine after a barium meal. Accordingly abdominal exploration was proceeded with on Feb. 25, 1941, through a right rectus incision. An obstructive lesion was encountered in the terminal portion of the ileum, just proximal to the ileocecal valve. The lesion was so bound down as the result of local infiltration that resection was deemed out of the question. Nodules, obviously metastatic, were felt and seen underneath the capsule of the liver, and firm, yellowish nodules of a similar character involved the nodes of the

ileocecal angle as well as the omentum. One of these nodules (omental) was removed for biopsy, and the operation was completed with a side to side ileotransversostomy designed as a short-circuiting procedure. Postoperative convalescence was extremely smooth, and the patient returned to his home on the nineteenth postoperative day. One year later his wife informed us by correspondence that he had gained 10 pounds (4.5 Kg.) and was able to do some work on the farm. She wondered if the condition was "really cancer."

The nodule removed for biopsy was firm and orange-yellow on section. Microscopically the routine hematoxylin and eosin stains of sections as well as several standard "silvering" technics left no doubt as to the diagnosis of grade 1 adenocarcinoma (carcinoid) (fig. 6 *a*).

CASE 3.—A single white woman aged 63 years first registered at the clinic on Dec. 11, 1940, because of "hot flushes and swelling of the face," of four years' duration. Her past medical history had been irrelevant. The only symptoms referable to her gastrointestinal tract were brought out by leading questions, in answer to which the patient admitted she was "occasionally bothered with cramps and that her appetite had been poor for several years." She had never suffered from constipation or diarrhea and had never noted blood in the stools. Her weight had been maintained fairly well.

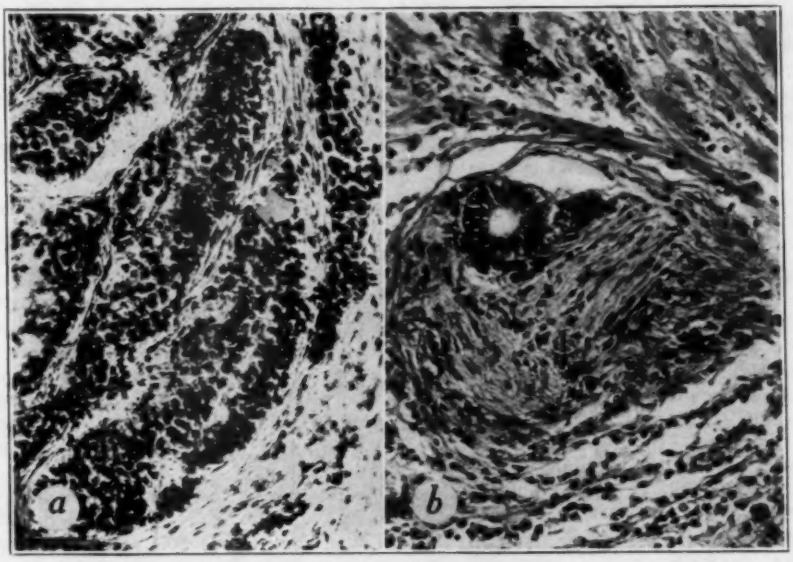

Fig. 6.—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin): In *a* (case 2) is seen an omental nodule showing dark-staining small cells grouped in cords and columns. Fibrosis is pronounced, and there are no acini present. The tumor is extremely cellular, and yet there are no mitoses (× 200). In *b* (case 3) is shown a tumor acinus formed within a perineural lymphatic space (× 145).

The essential finding on examination was a firm, nontender, somewhat movable mass, estimated to measure 6 cm. in diameter and located in the right lower quadrant of the abdomen. The mass did not move with respiration. Special dermatologic examination failed to reveal an actual cause for the attacks of facial erythema, but this condition was not believed to be related in any way to the intra-abdominal mass. Roentgenograms of the colon were interpreted as revealing a carcinoma in the region of the ileocecal valve.

Surgical exploration was performed on Dec. 16, 1940 through a primary right rectus incision. A neoplastic lesion was found involving the ileocecal region with nodular infiltration of the lymph nodes and other tissues in the ileocecal angle. Similar nodules were present throughout the liver. Resection of the portion of bowel containing the primary lesion was decided on after a fresh tissue diagnosis of carcinoid tumor. This resection included the removal of 15 cm. of the terminal portion of the ileum, the cecum, the appendix and most of the ascending colon. Included also in the operative procedure was a fairly wide excision of the mesentery of the ileum with nodes in the region of major involvement. Continuity was reestablished by means of side to side ileocolostomy following inversion of the resected ends by several rows of sutures. The patient after passing through a somewhat stormy convalescence finally returned to her home on the thirty-ninth postoperative day.

In a recent communcation her attending physician reported that the patient "had no complications and was really enjoying better health than one could expect."

The pathologic material consisted of 15 cm. of the terminal portion of the ileum, the cecum, the appendix and 20 cm. of ascending colon preserved in a 4 per cent solution of formaldehyde. Just at the ileocecal valve, partly in the cecum and partly in the ileum, was a firm, elevated, orange-yellow submucosal nodule measuring 3 by 3 by 2 cm., located on the mesenteric aspect as regards the ileum and showing a minimal amount of superficial ulceration. Mesenteric fat and mesenteric nodes in the ileocecal angle were obviously the seat of metastatic tumor deposits. On sectioning, the primary lesion was seen to involve both sides of the ileocecal valve in a "projecting" or semi-intussuscepting manner with evidence of obstruction manifested by some proximal dilatation of the ileum. No other lesions were found on careful examination of the remaining portions of the resected segments. The appendix was patent except at its tip and did not contain any carcinoids.

Salient microscopic features of this typical grade 1 adenocarcinoma (carcinoid) were as follows: (1) a minimal amount of superficial ulceration, the mucosa being thin and atrophic in appearance and covering all but the more central portions over the convexity of the tumor; (2) almost perfect reproduction of small acini by the tumor cells in the regions not affected by fibrosis (mucosal surface of tumor, several regional nodes, and certain of the perineural lymphatic spaces [fig. 6 *b*]); (3) absence of necrosis; (4) extensive fibrotic reaction around deeply located nests of tumor cells; (5) the occurrence of myohypertrophy in zones of tumorous invasion; (6) hypertrophy of nerve bundles in the mesenteric fat and invasion by tumor cells of the perineural lymphatic spaces; (7) invasion of blood vessels, and (8) true metastatic involvement of lymphatic nodes by the embolic route. In this, as in all other cases in which a segment of involved intestine was available for study, routine stains and other impregnation methods revealed the presence of Paneth and Kultschitzky cells in the "normal" mucosa.

CASE 4.[12]—A white garage mechanic aged 60 years registered at the clinic on July 2, 1926, complaining of "stomach trouble" of six months' duration. The illness took the form of repeated attacks of sharp pain in the upper portion of the abdomen. This pain occurred in attacks which came on from fifteen to twenty times daily and lasted but a few minutes. They were not related especially to the taking of food and were not accompanied by nausea, vomiting, diarrhea or constipation. However, the patient's appetite had been poor ever since the onset of the trouble, and a loss of 10 pounds (4.5 Kg.) had been sustained.

Appraisal of his physical condition resulted in a tentative diagnosis of abdominal carcinomatosis with enlargement of the liver and nodules in the anterior abdominal wall. The exact location of the primary lesion was not ascertained on roentgenoscopic examination of the stomach and colon. While the patient was being prepared for laparotomy, signs and symptoms suggesting a perforated abdominal viscus suddenly developed. That a perforation had in fact occurred was determined through a small incision which revealed gas and fluid in the peritoneal cavity. The condition of the patient was not such as to warrant even a minor attempt to localize the point of perforation, and accordingly drains were inserted. Death ensued twenty hours after operation.

Gross and microscopic features of the pathologic lesions in this case have been described previously by Cooke[6b] (case 3) and will not be repeated. Pathologic proof of extensive hepatic metastasis was an outstanding feature.

CASE 5.—A practicing Spanish physician aged 63 years first registered at the clinic on Dec. 1, 1941, with the complaint of repeated attacks of abdominal cramps during a period of three months. His family history was irrelevant. His past medical history included several attacks of amebic dysentery from which complete recovery had ensued. A right inguinal hernia had been repaired in 1939, at which time apparently nothing was found to indicate a malignant process involving the cecum.

The illness of which the patient complained had begun on Sept. 7, 1941, when he ate rather generously of an astringent fruit which necessitated the taking of much water. About eight hours later he was seized with severe crampy supra-umbilical pain. This lasted several hours in spite of treatment with camphorated tincture of opium. It was accompanied by much borborygmus and followed by nausea and vomiting. However, a purgation with milk of magnesia apparently relieved the gastrointestinal disturbance, and no further trouble ensued for two months. On Nov. 10, 1941, the aforementioned symptoms returned, but in a more or less subacute or chronic form. Some abdominal distention was noted, as was also the fact that the taking of food aggravated the abdominal distress. On one occasion severe cramping pain developed, and for a time it was feared that emergency laparotomy would have to be resorted to. However, once again the acuteness of the episode subsided to such a degree that roent-

12. This case was reported previously by Cooke.[6b]

genographic studies of the gastrointestinal tract were carried out. Results of these investigations indicated the presence of a lesion in the terminal portion of the ileum. Diverticuli were noted in the sigmoid portion of the colon. Examination of stools had failed to reveal any pathogenic amebas.

On examination at the clinic there was evidence of considerable loss of weight (7 Kg.). The abdomen was somewhat distended and tympanitic. No masses were palpable, but there appeared to be a localized zone of tenderness over the region of the cecum.

Roentgenograms of the stomach and cecum confirmed the information gained from a study of the previous roentgenograms. Inasmuch as the clinical history suggested a condition of intermittent intestinal obstruction, roentgenograms of the small intestine after a barium meal were not made.

At operation on Dec. 11, 1941, multiple, small, malignant-appearing nodules were found to involve the terminal portion of the ileum, the cecum and the first part of the ascending colon. Several nodes in the ileocecal angle were manifestly invaded. Accordingly resection was carried out, with removal of a portion of the terminal segment of the ileum, the cecum, the appendix and most of the ascending colon along with the local metastatic malignant deposits mentioned previously. Reestablishment of gastrointestinal continuity was effected by means of end to end

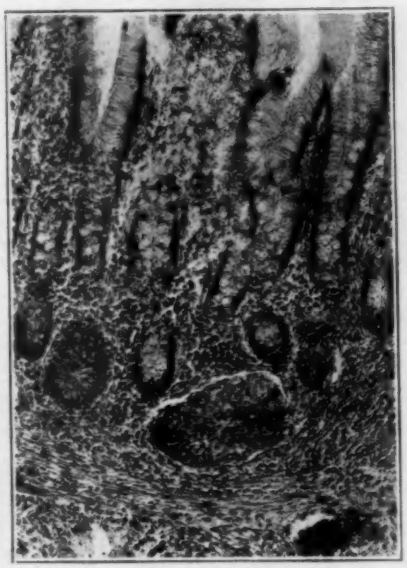

Fig. 7 (case 5).—Grade 1 adenocarcinoma (carcinoid) showing spread of tumor cells through mucosal lymphatics (hematoxylin and eosin; × 100).

ileocolostomy. Seventy-five grains (5 Gm.) of powdered sulfathiazole was dusted over the peritoneum in the region of the anastomosis, and the abdomen was closed with continuous sutures of S. M. chromic catgut. A transfusion of citrated blood was administered at the conclusion of the operation. Postoperative convalescence was normal, and the patient left the hospital on the eighteenth day. When he was last seen, in February 1943, there was no clinical evidence of recurrence of tumor.

Pathologic material consisted of 20 cm. of the terminal portion of the ileum, the cecum, the appendix and 20 cm. of ascending colon along with a group of ileocecal nodes and a generous apron of mesenteric and pericolonic fat. At the ileocecal valve, partly in the ileum and partly in the cecum, was a yellowish, firm, nodular tumor mass measuring 3 by 2 by 2 cm. This nodule showed only a small zone of superficial ulceration; the remainder appeared to be covered by a thin layer of mucosa; peripherally a certain degree of extension into the mesentery was apparent. Three centimeters proximally in the ileum was a similar but semipedunculated, intussuscepting, orange-yellow nodule 1.5 cm. in diameter and apparently independent of the first lesion. It too was firm in texture and appeared to be covered by a mucosal layer which was free from all but superficial ulceration. In the cecum at its junction with the ascending colon was a submucosal nodule 3 mm. in diameter, which might or might not be considered as entirely separate from the first lesion described. However, in the proximal portion of the

appendix were two submucosal nodules similar to the aforementioned but apparently separated from each other and from the larger lesions in the ileum and cecum; the terminal 6 cm. of the lumen of the appendix was obliterated and did not contain any tumors. Six nodes in the ileocecal angle were enlarged and firm. Metastatic involvement was evident from a typical orange-yellow color seen on sectioning. The only additional noteworthy feature consisted of a moderate dilatation of the ileum with thickening of the muscularis, proximal to the zone of malignant involvement.

Microscopically, for the most part, the various tumors duplicated the pictures described in connection with case 1. Invasion of veins was a noteworthy feature. A tendency to spread peripherally in the mucosal lymphatics was seen in several of the lesions (fig. 7). Pronounced hypertrophy of nerve bundles was apparent in connection with the largest nodule, and many of these nerve bundles were surrounded and invaded by cords of carcinoid cells.

CASE 6.—A white man aged 64 years visited the clinic on April 24, 1942, complaining of "stomach trouble." He had been well until 1933, when he began experiencing mild attacks of epigastric distress with distention. These attacks usually came on soon after eating, lasted several hours and then disappeared spontaneously. Dull pain, localized to the right of the umbilicus, occasionally accompanied these attacks. For several years the interval between consecutive episodes lasted one or two months, but thereafter it became shortened to a few weeks. Attacks became more severe and more definitely related to meals and were associated frequently with nausea. Relief by the use of alkalis was sought with moderate benefit only. In 1940, after the discovery of a mass in the abdomen, roentgenologic studies of the stomach and colon had been made. The seat of a healed duodenal ulcer was found, but it was not considered of much significance. Although no intrinsic lesion was found in the colon, fixation of the cecum was observed to be related to the abdominal mass, which was interpreted accordingly as being due to chronic inflammation—probably an old, resolved periappendical abscess. Surgical intervention therefore was not advised. The attacks of pain and discomfort continued and gradually assumed features indicative of subacute or chronic intestinal obstruction. There was considerable borborygmus; the passage of gas relieved the pain; the taking of food increased the discomfort and distention, and constipation was troublesome. However, in spite of all these symptoms the patient's general health suffered only mild deterioration, and there had been only a slight loss of weight.

Results of physical examination were essentially negative except for the finding of an enlarged prostate and the confirmation of a rounded, firm, nontender, semifixed abdominal mass estimated to measure 6 cm. in diameter and located just to the left of the umbilicus. Laboratory studies added little that was of diagnostic significance. Roentgenographic studies of the gastrointestinal tract were considered inadvisable in view of the patient's history. However, roentgenograms of the right renal region were useful in determining the extrarenal location of the aforementioned mass.

At operation on April 29, 1942 a malignant lesion was found in the terminal portion of the ileum. A huge, yellowish metastatic nodule involved the entire root of the mesentery. The liver contained similar yellowish nodules, obviously metastatic. Retroperitoneal lymph nodes also appeared to contain metastatic deposits, and one of these nodes was removed for biopsy. In spite of a fresh tissue diagnosis of grade 1 adenocarcinoma (carcinoid), it was judged that even a short-circuiting type of operation was out of the question, inasmuch as this would have meant sidetracking the entire small intestine to give relief from potential obstruction. Accordingly the incision was closed after exploration.

A recent communication from the patient read as follows: "It is now nine months since I left the clinic and my health is much improved over last year."

Pathologically the retroperitoneal node removed for biopsy proved typical of "carcinoid," with no noteworthy features except that it represented one of apparently many metastatic growths.

CASE 7.—A white traveling salesman aged 50 years registered at the clinic on April 7, 1924, complaining of crampy pains in the abdomen of six years' duration. Family and past medical records had been irrelevant except for an attack of typhoid fever from which the patient had suffered at the age of 16 years and from which recovery apparently had been complete.

The illness of which he complained had begun in 1918 with repeated attacks of mild to severe cramping pains in the midportion of the abdomen. These attacks had lasted for periods varying from hours to days and had been accompanied frequently by diarrhea and occasionally by the passage of dark-colored stools. The taking of food invariably had increased the severity of the pain and sometimes had resulted in regurgitation. Very little abdominal discomfort had been present between the attacks. Although the episodes had increased both in frequency and in duration over the period of the patient's illness, there had been surprisingly little deterioration of his general condition, and his weight had been maintained fairly well. Three weeks prior

to admission to the clinic appendectomy had been performed, and the surgeon had discovered a tumor involving the terminal portion of the ileum.

Results of physical examination were mainly negative except for the presence of mild abdominal distention. Laboratory studies added little of diagnostic import. In view of the surgical findings at the recent exploration it was deemed unnecessary to carry out roentgenographic examination of the gastrointestinal tract.

At exploration on April 15, 1924, a tumorous mass was located in the region of the ileocecal valve and short-circuited by means of a side to side ileocolostomy. On May 5, 1924, the growth was mobilized and removed along with 40 cm. of the terminal portion of the ileum, the cecum and most of the ascending colon. The procedure was planned so as to include in the resection a wedge-shaped portion of the mesentery which appeared to contain a number of indurated nodes at the ileocecal angle. No hepatic metastasis could be demonstrated by palpation. The severed ends of the ileum and colon were inverted as usual, and the abdomen was closed in layers. The patient made an uneventful convalescence and was alive nineteen years after operation.

The material for pathologic study consisted of 40 cm. of the terminal portion of the ileum, the cecum and 20 cm. of the ascending colon. Just above the ileocecal valve was an orange-

Fig. 8 (case 7).—Portion of a surgical specimen illustrating the "buckling" produced by small carcinoid tumors (possible roentgen sign).

yellow submucosal tumor measuring 4 by 3 by 2 cm., which projected into the ileum after the manner of an intussuscepting lesion, noticeably narrowing the lumen of the bowel at this point (fig. 8). Extension into the mesentery was apparent, as was also involvement of several lymph nodes at the ileocecal angle. In one of these, invasion by way of direct extension was apparent; in two nodes, situated at least 3 cm. from the nearest point of neoplastic extension, metastasis by way of lymphatic emboli seemed obvious. When the tumor was sectioned in a plane parallel to the longitudinal axis of the ileum, it was seen that involvement was mainly on the mesenteric aspect and that the muscularis propria was thrown up into the form of an inverted V, both sides of which were flanked by yellowish masses of tumor cells. This appearance further strengthened the conviction that the neoplasm had produced symptoms by causing intussusception. The ileum proximal to the point of obstruction was dilated and the muscularis presented evidence of work hypertrophy. An extreme degree of myohypertrophy was apparent in the zone of tumor infiltration. The cecum appeared normal on surface view. However, careful section of the mucosa brought to light a hitherto undiscovered yellowish nodule 3 mm. in diameter, entirely separate from the main tumor mass but demonstrating in miniature all the characteristics of an early carcinoid tumor.

Microscopic study of the ileocecal lesion did not bring to light any features which have not been described already in connection with cases 1 to 5. The cecal lesion was partly mucosal and partly submucosal, apparently independent in origin from the large growth and therefore

"innocent" according to the standards of those who regard most carcinoids as benign. Nevertheless, in this small growth actual beginning invasion of a fair-sized vein was observed (fig. 9).

CASE 8.—An automobile mechanic 50 years of age was referred to the hospital after admission to the clinic on Sept. 19, 1941. The illness that led to his admission was typical of an attack of acute appendicitis, of thirty-six hours' duration. The attack climaxed a series of several following his first in 1923. Between attacks the patient had been in good health. A six year history of constipation with occasional bloating might or might not have been interpreted as being of importance in the light of subsequent observations. (This history was obtained by questioning the patient after his operation.)

Exploration performed through a primary McBurney incision on the right side revealed, in addition to an acutely inflamed condition of the appendix, a tumor involving the terminal portion of the ileum. Accordingly the primary incision was closed and a right rectus incision made. One stage removal of the terminal portion of the ileum, the cecum, the appendix and the ascending colon was performed, with inclusion of a generous segment of mesentery ascertained to contain a number of enlarged, indurated nodes. End to end ileocolostomy reestablished gastrointestinal continuity. Raw surfaces were peritonized carefully, and 5 Gm. of sulfanilamide powder was dusted about the line of anastomosis. Postoperatively a transfusion of

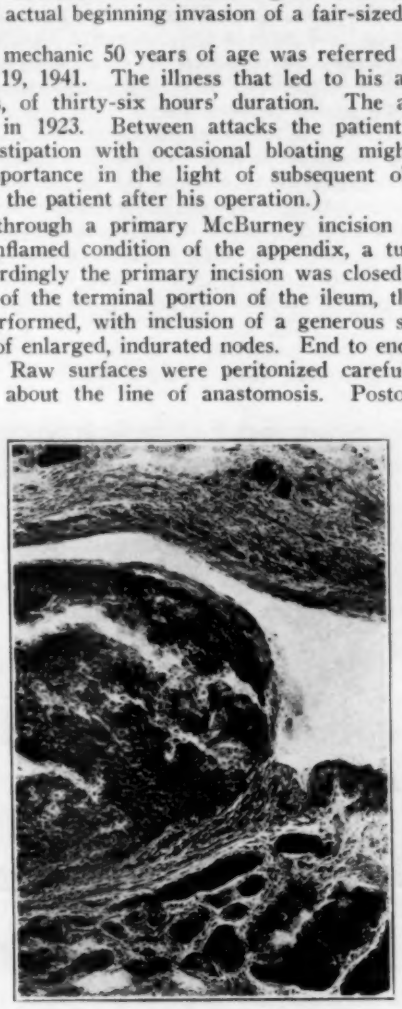

Fig. 9 (case 7).—Grade 1 adenocarcinoma (carcinoid). This small tumor had not metastasized and accordingly would be considered benign by some. However, note beginning invasion of a large venous channel. (Hematoxylin and eosin; × 100.)

citrated blood was administered. After a somewhat stormy convalescence the patient left the hospital one month postoperatively. At the end of a twenty month period of subsequent observation he had not experienced any recurrence of trouble.

The operative material consisted of 20 cm. of the terminal portion of the ileum with an attached portion of the mesentery, the cecum, the appendix and 15 cm. of the ascending colon. Grossly the appendix was inflamed acutely but unperforated. In the ileum, 5 cm. above the ileocecal valve and on the mesenteric aspect, appeared a firm, orange submucosal nodule measuring 2 by 2 by 0.5 cm. No ulceration was apparent. The lumen of the ileum was somewhat narrowed at the level of the tumor and was mildly dilated proximally. Sections through the tumor revealed central extension into the mesentery. Peripheral invasion of the muscularis and the peritoneum was apparent, with puckering of the former and moderate hypertrophy of the latter. Eight regional nodes appeared to be involved by tumor, and in three of these the possibility of spread by direct extension was precluded by a location at some distance from the nearest point of infiltration. No tumorous involvement was found in the cecum or in the appendix.

Microscopically the lesion was a typical carcinoid. Unusual features were a relative lack of fibrosis about groups of tumor cells in the regional lymphatic nodes and the formation within these nodes of tumor acini (fig. 10 *a*). Some slight variation of size of nuclei also was observed, with occasional multinucleated forms. These were taken to represent a process of amitotic division (the apparent mode of "reproduction" in carcinoid tumors) and the lesion accordingly was still classified as a grade 1 adenocarcinoma (Broders).

CASE 9.—A white married woman aged 39 years registered at the clinic on Oct. 26, 1931, because of pain in the right lower quadrant of the abdomen of ten months' duration. She had been well until the late summer of 1930, when a swelling had appeared in the abdomen. Operation had been performed with the removal of "double ovarian cysts," which she was assured were benign. Ever since her operation the patient had been conscious of a dragging pain in the right lower abdominal quadrant. Severity of the pain varied considerably, but it was never sharp enough to require morphine for relief, and although several of the more recent episodes had been accompanied by borborygmi, no change had been noted in her intestinal "habits." Her appetite had remained good, and there had been no appreciable loss of weight.

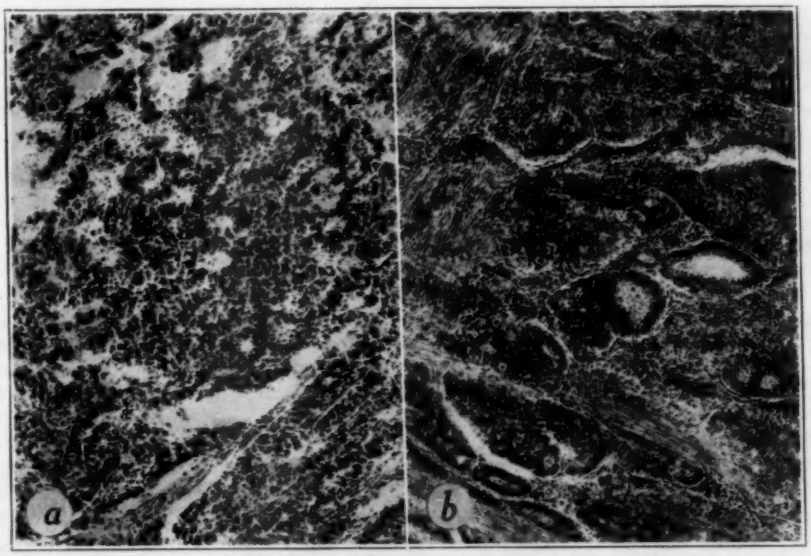

Fig. 10.—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin; × 100): In the nodal metastasis seen in *a* (case 8) fibrosis is minimal and the cells are differentiating to form acini; we do not believe these spaces represent rosettes. In *b* (case 9) is seen the mucosal surface of a tumor showing numbers of rounded and angular acini; the latter form is important in identifying these hollow structures with true acini and is an important index of cellular differentiation.

The essential discovery on physical examination was a small, semifixed, slightly tender mass situated in the right lower abdominal quadrant and ascertained on bimanual pelvic examination to be somewhat adherent to the right side of the uterus. Results of laboratory examination of blood and urine were normal. Roentgenograms made of the colon were interpreted as not revealing any intrinsic abnormality, but the terminal portion of the ileum was poorly visualized on the roentgenograms. At operation on Oct. 28, 1931, the diagnosis of adenocarcinoma (carcinoid) was made by means of biopsy of a mesenteric node. The primary lesion, located in the terminal portion of the ileum, was accordingly short-circuited through a side to side ileotransversostomy. Appendectomy was performed. On Nov. 23, 1931, the growth was mobilized and removed along with the portions of the ileum, the cecum and the colon between the limbs of the former anastomosis. The open ends of the ileum and colon were inverted in the usual manner. Because of the poor condition of the bowel, performance of an additional ileocolostomy was necessary. The patient returned to her home one month later. When she returned to the clinic in May 1932 she stated that she had continued to have some abdominal distress with bouts of diarrhea. However, there was no

unequivocal evidence of a recurrence of her malignant process, and the diarrhea responded satisfactorily to dietary regulation plus the use of kaolin. Supplementary vitamins also were prescribed.

On June 17, 1936, a communication from her attending physician stated that a large fixed tumor involving the left upper portion of the abdomen had developed. It was his considered opinion that the mass was malignant. Death occurred on Nov. 23, 1936.

Pathologic material consisted of the mesenteric node and the appendix removed at operation on Oct. 28, 1931, and 40 cm. of the terminal portion of the ileum, the cecum, the ascending colon and a portion of the transverse colon from the operation on Nov. 23, 1931. Grossly and microscopically the appendix presented the changes of chronic appendicitis. No tumor nodules were found. The firm, orange mesenteric node was typical of carcinoid tumor. In the submucosa of the ileum, just proximal to the ileocecal valve, was a firm, yellowish orange nodule 2 cm. in diameter and presenting a small region of shallow mucosal ulceration. Previous sectioning of the specimen made it impossible to ascertain the exact relation of the growth to the mesenteric attachment and the degree of obstruction produced. Indirect evidence for obstruction was seen in the proximal portion of the ileal segment where dilatation of the lumen was present with thickening of the muscular coat. Infiltration of the mesentery was observed and several nodes appeared to be metastatically involved. Lesions were not observed in the cecum or the colon.

An interesting microscopic feature, in addition to the nodal metastasis and the invasion of several perineural lymphatic spaces and one small venous channel, was the finding in the mucosa of almost perfect tumor acini. These demonstrated oval as well as rounded lumens, and in some portions it was difficult to decide which acini were tumorous and which belonged to the glands of the normal mucosa (fig. 10 *b*).

Case 10.—A white man aged 65 years visited the clinic on Dec. 4, 1939, complaining of pain in the abdomen of seven years' duration. His family and past medical histories contained no pertinent data. The illness of which he complained had begun seven years previous to registration with recurrent attacks of "knifelike pain" localized to the right midportion of the abdomen. These attacks of pain, which came at three to four month intervals, would last for ten to thirty minutes and usually were accompanied by nausea and occasional vomiting. Vomiting seemed to relieve the pain. Three years prior to the patient's admission to the hospital the character of the pain had changed to a dull ache which was more or less continuous. The location also shifted, the maximal discomfort changing to the right lower abdominal quadrant. Vomiting became infrequent. Six months prior to registration diarrhea had developed. This had continued in an episodic manner with an average of six to ten stools daily. Blood had never been noticed. A loss of some 20 pounds (9.1 Kg.) had been sustained over a twelve month period prior to admission.

Examination disclosed a somewhat ill-appearing white man suffering from mild abdominal distention. Peristalsis was visible through a thin abdominal wall. In the right lower quadrant of the abdomen a large mass was palpable, and the tissues in the abdominal parietes overlying the mass were locally indurated and somewhat nodular. The joints of the fingers, hands and ankles were somewhat swollen and stiffened in what was interpreted clinically as chronic infectious arthritis. Laboratory studies revealed the presence of gastric achlorhydria and mild secondary anemia. Albuminuria was graded 1 (on the basis of 1 to 4). Roentgenograms of the stomach and colon did not reveal any intrinsic abnormality.

At exploration on Dec. 9, 1939 a mass was found involving the terminal portion of the ileum and the regional nodes. Coils of intestine were matted together in the vicinity of the growth. No definite metastasis could be palpated in the liver, but numerous "implants" were present in the omentum and over the parietal peritoneum. One of these implants was removed for biopsy. Inasmuch as the patient stood the operation poorly, and in view of the fact that the clinical signs of intestinal obstruction were rather mild, it did not seem advisable to proceed with a short-circuiting type of operation. The incision was accordingly closed after exploration.

The material available for pathologic study consisted of a small nodule of tissue removed from the peritoneum of the anterior abdominal wall. The yellow color and firm texture were typical of carcinoid tumor. Microscopic sections on slides were prepared by routine methods and by the silver impregnation technic. No nerves appeared in the sections, and the veins did not appear to be involved. Pronounced fibrosis was evident about the clumps of tumor cells.

Case 11.—A white woman aged 57 years registered at the clinic on Nov. 27, 1930, complaining of symptoms referable to carcinoma of the rectosigmoid. After preliminary colostomy on Dec. 1, 1930 the growth was removed by posterior resection. Radium needles were inserted in the posterior wound with a view to controlling the spread of local metastatic deposits which were ascertained to be present around the bases of the broad ligaments. The growth proved

to be an infiltrating grade 2 (Broders) adenocarcinoma of the type ordinarily seen in the colon and rectum. Nodes were involved metastatically. The carcinoma recurred locally, and the patient subsequently returned on several occasions for further therapy with roentgen rays and radium. However, her condition progressively deteriorated, and death ensued on Nov. 6, 1931.

At necropsy an independent carcinoid tumor measuring 1.5 cm. in diameter was found involving the terminal portion of the ileum just lateral to the mesenteric aspect. The growth was submucosal and yellow, but although productive of local scarring resulting from peritoneal extension, it had not compromised the lumen of the ileum materially. Two regional mesenteric nodes were firm and yellowish and obviously represented metastasis. It was the consensus that the lesion in the ileum, however interesting, had not contributed materially to the patient's death. The case illustrates again how a carcinoid may metastasize at an early stage of its evolution.

Microscopic features worthy of note were the lack of deep ulceration over the eroded surface of the growth, the "discontinuous" type of spread to the regional nodes (constituting therefore a true metastasis), the presence of granular cells in the mucosa of uninvolved portions of the ileum and the presence of occasional droplets of mucus within the lumens of tumor acini (fig. 11 *a*). The ileal tumor was quite dissimilar to the lesion in the rectosigmoid.

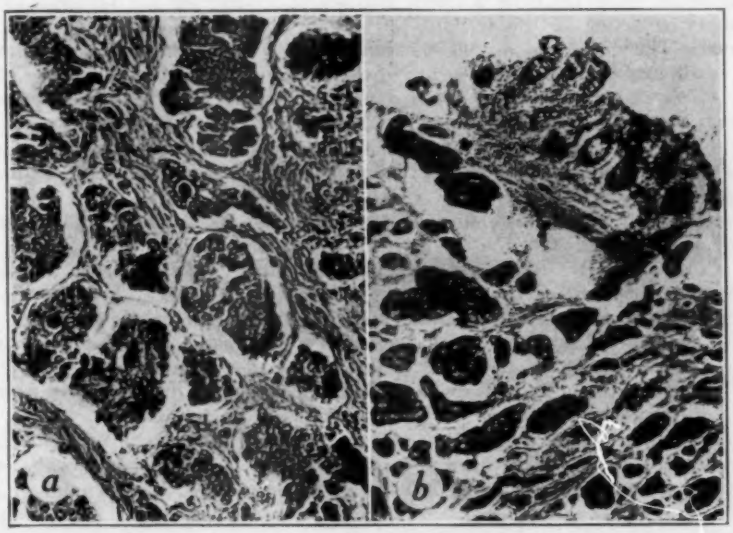

Fig. 11.—Grade 1 adenocarcinoma (carcinoid): In *a* (case 11) mucus, a rare finding in carcinoids, is depicted within three tumor acini (Galantha mucus stain; × 195). In *b* (case 12) mucosal cells at the bases of crypts and cells of underlying tumors show blackening of argentaffin granules. (Bielschowsky method; × 100.)

CASE 12.—An obese, multiparous woman aged 55 years visited the clinic on July 9, 1920, suffering from symptoms referable to a recurrent incarcerated umbilical hernia which had twice been reduced and repaired surgically. The hernia was again repaired but later again recurred. The patient succumbed at the age of 65 years after an episode of incarceration of her hernia. For five years prior to her death she had been suffering from moderately severe diabetes.

At necropsy several loops of gangrenous bowel were found in the recurrent hernial sac. Generalized peritonitis was present. Two orange-yellow submucosal nodules measuring 1.5 cm. and 8 mm. in diameter, respectively, were found in the ileum just above the ileocecal valve and nearer the mesenteric than the antimesenteric border of the ileum. Several nodes in the adjacent mesentery appeared grossly to be involved metastatically.

Microscopically both lesions proved to be typical grade 1 adenocarcinomas of the carcinoid type. Some superficial ulceration was present in the case of the larger lesion, but a thinned-out mucosa invested the surface of the smaller tumor. Impregnation of the tissues with silver (Bielschowsky method) produced a pronounced blackening of the cytoplasm of all the tumor cells and of the granular cells in adjacent zones of normal mucosa (fig. 11 *b*). Involvement

of the regional nodes appeared in this case to obtain, possibly on the basis of direct extension from the primary (larger) lesion. Lymphatics of the mesentery were permeated, but actual invasion of blood vessels was not observed. Of outstanding interest was the occasional production of small droplets of mucus demonstrated within the tumor acini by the Galantha method of staining for mucus. This phenomenon is to be interpreted in the light of incontestable evidence that carcinoids are of entodermal origin.

CASE 13.—A white woman aged 68 years came to the clinic on Sept. 8, 1931, complaining of "stomach trouble" of five months' duration. Her past medical history had been irrelevant. The illness of which she complained was described as an unusual "heaviness" in the midportion of the abdomen associated with belching and flatulence. Distress had been more or less constant but had been aggravated by the ingestion of food. She did not complain of any pain, nausea or vomiting, but an intermittent diarrhea, without blood, had been present since the onset of her other symptoms. In addition, there had been a loss of some 20 pounds (9.1 Kg.) over a four month period prior to registration.

On examination, emaciation of moderate degree was present. A semifixed mass, estimated to measure 8 cm. in diameter, was palpated in the right lower quadrant of the abdomen. Laboratory studies did not reveal anything of diagnostic significance, and roentgenograms of the stomach and colon were interpreted as being "negative for intrinsic disease."

At operation on Sept. 18, 1931, a tumor was found obstructing the terminal portion of the ileum. Primary resection of the terminal 40 cm. of the ileum, which contained the tumor, was performed. The distal end of the remaining portion of ileum was inverted and a lateral anastomosis made between it and the cecum in the region of the ileocecal valve. The appendix was normal in appearance and was not disturbed. Postoperative convalescence was normal, and the patient was dismissed from the hospital on the twentieth postoperative day.

Subsequent correspondence with the patient's attending physician revealed that "palpable liver metastasis developed within a period of months, and the patient died a routine carcinoma death in October 1933."

Pathologic material consisted of 40 cm. of the terminal portion of the ileum along with a small amount of mesenteric fat. No nodes were found on the specimen. Fifteen centimeters from the distal cut end of the ileum was an indurated, yellow, flat submucosal nodule measuring 1.5 cm. by 1 cm. by 5 mm. This nodule, which was located halfway between the mesenteric and the antimesenteric aspect of the bowel, appeared on section to infiltrate the wall as far as the serosa. Some local puckering and induration were present, and obstruction was evident in the form of thickening of the ileal musculature proximal to the growth. The mesentery of the ileum in the region of the growth did not appear grossly to be invaded by the tumor, whose nearest edge lay fully 2 cm. distant.

Microscopic sections made through the growth had the typical characteristics of grade 1 adenocarcinoma (carcinoid) as outlined for previous cases. Noteworthy local features were the almost intact condition of the superficial layer of the mucosa, the presence of one or two regions in which an origin of carcinoid cells could be traced to the bases of crypts and apparent myohyperplasia of the infiltrated muscularis propria. In keeping with the ultimate outcome of the case was the unexpected finding of strands of carcinoid cells infiltrating through the lymphatics of the mesentery, filling especially the perineural spaces in a veritable carcinomatous "neuritis." This mode of spread appeared to obtain on a true metastatic (embolic) basis, as no definite direct connection could be traced between the primary lesion and the mesenteric deposits.

ANALYSIS OF CLINICAL DATA

Incidence.—In the present series, carcinoid tumors comprised 23 per cent of all malignant neoplasms affecting the small intestine. The latter, according to Mayo and Nettrour,[13] made up 0.47 per cent of all malignant neoplasms found in the entire gastrointestinal tract. Ariel,[6a] in a comparable series, observed an incidence of 0.021 per cent for ileal carcinoid tumors. The incidence of appendical carcinoid tumors, as previously reported from this clinic by MacCarty and McGrath,[14] was 0.47 per cent of all surgically removed appendixes. According to the literature localization in the appendix is two to ten times as frequent as in the

13. Mayo, C. W., and Nettrour, W. S.: Carcinoma of the Jejunum, Surg., Gynec. & Obst. **65**:303-309 (Sept.) 1937.

14. MacCarty, W. C., and McGrath, B. F.: The Frequency of Carcinoma of the Appendix: A Report of Forty Cases, Ann. Surg. **59**:675-689 (May) 1914.

ileum, while involvement of the stomach, duodenum, jejunum, Meckel's diverticulum, colon and rectum is uncommon.

Age.—The youngest patient in this series was 39 and the oldest 78 years of age; the average age was 58 years. This corresponds closely to the observation of Cooke,[6b] who noted, on analyzing the literature, that the average age of patients who had metastasizing carcinoid tumors of the small intestine was 57.2 years. In the same analysis Cooke gave as 54.3 years the average age for 83 patients who had nonmetastasizing carcinoid tumors of the small intestine. The average age of patients who had appendical carcinoid tumors, on the other hand, was listed as 30 years by MacCarty and McGrath.[14] The aforementioned observations accordingly lend support to the view early expressed by Burckhardt [15] that metastasis from carcinoid tumors is merely a matter of time.

Sex.—In the present series 8 of the patients were men and 5 were women, a ratio which seems to have obtained throughout the literature on ileal carcinoid tumors. However, it appears that appendical carcinoid tumors are considerably more common among women than among men.

Symptoms.—Symptoms referable to "disturbed intestinal function" had been present in no less than 9 of the 13 cases in the present series (table 1) for an average duration of forty-two months. This incidence is high, if judged comparatively from reports in the literature. Cooke found the incidence to be 50 per cent for metastasizing carcinoid tumors but pointed out that pertinent clinical details were lacking in many of the remainder. A history suggestive of chronic, slowly progressive, intestinal obstruction was elicited from 8 patients. In contrast to a comparable group of cases of the "ordinary" type of ileal adenocarcinoma,[16] these obstructive symptoms were usually mild, and the patients, on examination, appeared relatively well nourished. Obstructive features in these 8 cases often were described as episodic with crampy abdominal pain coming on in attacks, sometimes related to ingestion of food and occasionally relieved by regurgitation. Distention characteristically accompanied these attacks, which recurred with increasing frequency. Constipation was present in 3 cases, moderate to severe diarrhea in 2 and mild "looseness" in 1. In 6 cases one or more abdominal masses were clinically palpable. These masses were variously located, were semifixed, did not move with respiratory excursions of the diaphragm and were not tender or were only slightly tender. Melena, a symptom commonly observed in the "ordinary" type of ileal carcinomas and in malignant myomas, was observed in only 1 of our cases, and its origin was attributed to hemorrhoids. The infrequency of this symptom was in keeping with a notable absence of anemia.

In 3 of the cases there were no symptoms to indicate the presence of a lesion in the gastrointestinal tract. This group, however, represented a minority. It has become increasingly evident from the literature that one must abandon the original conception of carcinoid tumors as clinically silent neoplasms. Moreover, disturbances of major proportions have been recorded as resulting from carcinoid tumors which had not metastasized.

Laboratory findings, including the results of chemical examination of the blood, were not particularly helpful except as corroborative evidence supporting the clinical diagnosis of mild chronic intestinal obstruction. Hematologic studies rarely revealed any pronounced degree of anemia. Examination of stools for occult blood usually demonstrated traces of the latter, but in no instance were the

15. Burckhardt, J. L., cited by Cooke.[6b]

16. Mayo, C. W.: Malignancy of the Small Intestine, West. J. Surg. **48**:403-407 (July) 1940.

stools, on examination, described as being tarry. These negative findings stood in observed contrast to those associated with "ordinary" types of carcinoma of the ileum, and in retrospect, therefore, they should perhaps be regarded as having been of some significance.

In the cases of more subacute obstruction in this series roentgenographic studies of the gastrointestinal tract were deemed inadvisable. In several instances in which the lesion involved the terminal portion of the ileum the presence of a deformity of the ileocecal valve suggested, but in no case actually decided, the nature of the lesion. Recently Miller and Herrmann [17] described a roentgenologic sign which enabled them in 1 instance to arrive at the correct preoperative diagnosis of ileal carcinoid tumor. Acute "buckling" or kinking of the bowel is a common finding in cases in which carcinoid tumors have infiltrated the serosa. Although other lesions occasionally give rise to the same phenomenon, carcinoid tumor is the only *small* nonulcerated submucosal tumor in which this sign may be elcited. Reviewing in the literature the gross illustrations of "buckling" carcinoid tumors, one can see readily the possibilities for the use of Miller and Herrmann's sign in the preoperative diagnosis of a tumor which heretofore has always awaited indentification by the pathologist.

Treatment.—In a relatively large number of our cases (85 per cent) the condition was a primary surgical problem, only 2 of the tumors being "accidental" necropsy findings. In 3 of the 11 cases in which operation was performed, the operation was confined to exploration with biopsy, because of widespread intra-abdominal metastasis and fixation of coils of intestine. In 1 case, in addition to the aforementioned procedure ileocolostomy was possible with short-circuiting of the growth. In 5 of the 7 remaining cases, one stage resection was effected even though 3 patients had hepatic metastasis at the time of operation. In 2 cases, operative removal in two stages was dictated by the general condition of the patient. Surgical treatment in every case was designed to be as radical as possible under the circumstances. Whereas one might have been chary of performing more than ileocolostomy for "ordinary" carcinoma of the ileum with hepatic metastasis, evidence has been afforded that in the case of carcinoid tumors growth of metastatic deposits may become "stationary" [18] following removal of the primary tumor. Horsley [19] advocated resection in cases of carcinoid tumor with metastasis, an opinion in which others concur. In these circumstances the pathologist familiar with methods of diagnosis by fresh frozen sections can offer valuable assistance to his surgical colleague.

Prognosis.—The life history of carcinoid tumors is one of slow evolution, with a long preoperative phase and with surprisingly long postoperative survival of patients so afflicted. Among the 11 cases in the present series in which operation was performed, 1 patient died several days after biopsy for an inoperable tumor, 2 patients succumbed two and five years after operation respectively, apparently as a result of local recurrence and metastasis, but the remaining 8 patients were living and "surprisingly well" for periods varying from ten months to nineteen years (table 1) even though several had hepatic metastasis. This parallels the experience of Terplan, Weintraub and Wolf,[18] whose patient survived five years after ileocolostomy for carcinoid tumor with hepatic involvement. The death of

17. Miller, E. R., and Herrmann, W. W.: Argentaffin Tumors of the Small Bowel: Roentgen Sign of Malignant Change, Radiology **39**:214-220 (Aug.) 1942.

18. Terplan, K.; Weintraub, D., and Wolf, N. J.: Stationary Metastasizing Carcinoid of the Ileocecal Valve, Arch. Path. **30**:1155 (Nov.) 1940.

19. Horsley, J. S.: Carcinoma of the Jejunum and of the Ileum, J. A. M. A. **117**:2119-2123 (Dec. 20) 1941.

their patient occurred as a result of drowning, and at necropsy the "stationary" hepatic metastasis had not increased appreciably in size. Stewart and Taylor's [20] patient was alive ten years after development of metastasis, and Mallory [21] recorded a similar case in which the patient survived for twenty years. Cameron [22] stated that no less than 33 per cent of patients are alive at the end of eight years after operation for metastasizing carcinoid tumor. Thus, while death occurs as a result of carcinoid tumor (14 deaths from 1930 to 1939 according to Ariel's analysis of the literature), the outcome sometimes may be retarded by the simple procedure of ileocolostomy if surgical removal of the growth is impossible. Moreover, it has been suggested recently that postoperative roentgen therapy [23] may improve a prognosis which at worst is notably better than the outlook with the "ordinary" type of carcinoma of the small intestine.

TABLE 1.—*Metastasizing Carcinoid Tumors: Comparative Clinical Data*

Case	Sex	Age, Years	Symptoms and Findings	Duration	Operative Procedure	Outcome
1	M	42	Obstruction; diarrhea (mass present)	5 yr. 3 yr.	Primary resection	Well 28 months
2	M	78	Episodic obstruction	4 mo.	Exploration ileocolostomy	Well 1 year
3	F	63	"Cramps" and poor appetite (mass present)	2 yr.	Primary resection	Living 27 months
4	M	60	Crampy abdominal pain in attacks (masses present)	6 mo.	Exploration	Death (rupture of intestine)
5	M	63	Crampy abdominal pain in attacks	3 mo.	Primary resection	Living and well 14 months
6	M	64	Abdominal distress; pain; distention in attacks (mass present)	9 yr.	Exploration only	Living 9 months
7	M	50	Crampy abdominal pain in attacks	6 yr.	Preliminary ileocolostomy; secondary resection	Living 19 years
8	M	50	None (?) (mild constipation)	.....	Primary resection	Well 20 months
9	F	39	Dragging pain (mass present)	10 mo.	Ileocolostomy; secondary resection	Died 60 months
10	M	65	Crampy abdominal pain in attacks (mass present)	7 yr.	Abdominal exploration	Unable to trace
11	F	57	None	.....	Nonoperative	Necropsy observation
12	F	65	None	.....	Nonoperative	Necropsy observation
13	F	68	Intestinal obstruction in attacks; diarrhea (mass present)	5 mo.	Primary resection	Death from carcinoma 2 years

PATHOLOGIC DATA

Location of Lesion or Lesions (table 2).—In all 13 cases the ileum was the primary seat of formation of tumor. In several instances in which multicentric nodules were present, additional points of localization were as follows: jejunum, 1 case; cecum, 1 case; cecum and appendix, 1 case. Among 9 cases in which the primary

20. Stewart, M. J., and Taylor, A. L.: Carcinoid Tumor of Appendix with Large Pelvic Deposits, J. Path. & Bact. **29**:136-139, 1926.

21. Multiple Carcinoids of Ileum with Regional Metastases, Cabot Case 26162, New England J. Med. **222**:684-687 (April 18) 1940.

22. Cameron, A. L.: Primary Malignancy of Jejunum and Ileum, Ann. Surg. **108**:203-220 (Aug.) 1938.

23. Bailey, O. T.: Argentaffinomas of the Gastrointestinal Tract, Benign and Malignant, Arch. Path. **18**:843-864 (Dec.) 1934. Klemperer, P., in discussion on Goldberg, S. A.: Unusual Neoplasms of the Small Intestine, Am. J. Path. **14**:663-664 (Sept.) 1938.

lesion could be localized definitely to a particular segment of intestine, this point of origin was the terminal portion of the ileum in 3 cases and the ileocecal valve in an additional 3. These findings are in keeping with the observations of Cooke [6b] and of Raiford [6f] that the majority of ileal carcinoid tumors seem to have a predilection for the terminal segment of the small intestine. None of these metastasizing carcinoid tumors originated in connection with Meckel's diverticulum. Hertzog and Carlson,[24] however, have reported from this clinic 2 nonmetastasizing carcinoid tumors thus originating.

Multicentricity.—Multiple carcinoid tumors occurring simultaneously in the same segment or in adjacent segments of intestine are regarded as multiple primary growths rather than as the result of metastatic spread from a single focus. In the

TABLE 2.—*Metastasizing Carcinoid Tumors: Comparative Pathologic Data*

Case	Location	Multicentric	Relation to Mesentery	Size	Nodes and Fat (Involvement)	Nerves and Blood Vessels	Peritoneum and Liver *
1	Ileum	+ (68)	Variable	2 mm. to 3 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver +*
2	Ileum	?	?	Large †	Nodes +* Fat +	Nerves ? Vessels ?	Peritoneum + Liver +*
3	Ileocecal valve	0	Mesenteric	3 by 3 by 2 cm.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver +*
4	Ileum and jejunum	+ (15)	Variable	0.5 to 1.5 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver +
5	Ileum; cecum; appendix	+ (5)	Antimesenteric	2 mm. to 3 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver —
6	Ileum	?	?	Large †	Nodes + Fat +*	Nerves — Vessels —	Peritoneum + Liver +*
7	Ileocecal region; cecum	+ (2)	Mesenteric	4 by 3 by 2 cm. and 3 mm. diam.	Nodes + Fat +	Nerves ? Vessels +	Peritoneum + Liver —
8	Ileum (terminal)	0	Mesenteric	2 by 2 by 0.5 cm.	Nodes + Fat +	Nerves + Vessels —	Peritoneum + Liver —
9	Ileum (terminal)	0	?	2 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver —
10	Ileum	?	?	Large †	Nodes ? Fat +	Nerves ? Vessels ?	Peritoneum + Liver —
11	Ileum	0	Paramesenteric	1.5 cm. diam.	Nodes + Fat —	Nerves — Vessels —	Peritoneum + Liver —
12	Ileum (terminal)	+ (2)	Paramesenteric	1.5 cm. and 8 mm. diam.	Nodes + Fat +	Nerves — Vessels —	Peritoneum + Liver —
13	Ileum	0	Paramesenteric	1.5 by 1 by 0.5 cm.	Nodes — Fat +	Nerves + Vessels —	Peritoneum + Liver —

* Ascertained at surgical exploration. No biopsy.
† Surgical description.

present series such a multicentric mode of origin was demonstrated in 5 of the 10 cases in which accurate information was available on this point. In 1 instance it was necessary to search rather carefully for the second tumor nodule, which lay semiconcealed beneath the mucosa of the cecum. Thus we confirmed the impression of other investigators who have estimated that 20 to 50 per cent of ileal carcinoid tumors occur as multiple tumors. The number of independent nodules in this series of cases varied from two to sixty-eight. In a search of the literature we have not found a record of any instance in which the number of nodules exceeded that demonstrated by our case 1. Multicentricity of ileal carcinoid tumors is a phenomenon which, although poorly understood as regards causation, nevertheless carries very clear implications from the standpoint of surgical treatment. More specifically, great care should be exercised at the time of operation to make

24. Hertzog, A. J., and Carlson, L. A.: Carcinoid of Meckel's Diverticulum, Arch. Path. **20**:587-589 (Oct.) 1935.

sure that the limits of resection are extended widely enough so as to include all of the neoplastic nodules.

Relation of Tumor to Mesentery.—It has been stated [8] that carcinoid tumors of the small intestine invariably arise along the antimesenteric border. In the present series, 9 of the specimens were in a state of preservation such as to allow one to determine the localization of the tumor in relation to the circumference of the ileum. In 2 instances the point of origin was exclusively antimesenteric, in 3 it was definitely mesenteric, in 2 it was paramesenteric and in the remainder a variable relation existed. It is therefore our opinion that carcinoid tumors may arise from any point along the circumference of the small intestine.

Size of Tumor.—Carcinoid tumors have been aptly termed "little carcinomas," but occasionally large specimens are encountered. The tumor in one of Bretschger's [25] cases was as large as a child's head. In the present series the largest of the primary tumors available for measurement was 4 by 3 by 2 cm. and the smallest 2 mm. in diameter. Our own material confirmed the view expressed by others that the metastatic deposits from carcinoid tumors frequently exceed in volume the primary nodules. Size was related to metastasis in a general way only, and some of the ileal carcinoid tumors not included in this series were larger than some in which metastasis had occurred.

Color of Tumor.—Carcinoid tumors are described almost universally as being yellowish.[26] All of the tumors in the present series were more orange than yellow. Mallory [27] too described carcinoid tumors as orange-yellow nodules and compared their color to that of the adrenal cortex. MacCarty and McGrath [14] made a similar colorimetric distinction in connection with appendical carcinoid tumors. Whether or not carcinoid tumors are fundamentally yellow or orange, we believe that their color is so characteristic that it may often serve as an important factor in gross diagnosis at operation. A notable lack of necrosis is also useful in distinguishing these from other malignant tumors of the small intestine.

Mucosal Relation.—It is generally stated that carcinoid tumors are submucosal and are unassociated with superficial ulceration. Some authors state definitely that ulceration is never observed; others, including the majority, admit that ulceration is present but in the microscopic rather than the gross sense of the word. In the present series gross superficial ulceration was present in all of the larger nodules examined. In some of the smaller nodules ulceration was not obvious on gross inspection, but in nearly every instance microscopic sections demonstrated that the tumor cells had broken through to the surface at one or more points. It must, however, be emphasized that the ulceration present was shallow, with minimal amounts of necrosis and never with the overhanging edges so commonly seen in other types of gastrointestinal carcinoma. This fact has a most important bearing on symptomatology, as it explains why melena is rarely observed in connection with carcinoid tumors.

Relation to the Peritoneum and Muscularis.—Carcinoid tumors have great propensities to invade, being similar in this respect to "cylindromas" (which they indeed resemble otherwise).[28] It is thus not surprising that muscularis mucosae,

25. Bretschger, E.: Klinik und Prognose der Appendix- und Dünndarmcarcinoide, Deutsche Ztschr. f. Chir. **249**:297-316, 1937.

26. Huebschmann, cited by Cooke.[6b] Bailey.[23]

27. Carcinoid of Ileum, Cabot Case 26192, New England J. Med. **222**:806-808 (May 9) 1940. Footnote 21.

28. Dockerty, M. B., and Mayo, C. W.: Primary Tumors of the Submaxillary Gland with Special Reference to Mixed Tumors, Surg., Gynec. & Obst. **74**:1033-1045 (June) 1942.

the submucosa, the muscularis propria and the peritoneum are invaded frequently by carcinoid cells. (Some investigators, including Cooke,[6b] have accepted peritoneal invasion as a criterion of metastasis. We have not so regarded this direct mode of spread.) In the present series the muscularis mucosae was pervaded by tumor cells even in the smallest tumors, the majority of whose cells lay beneath this layer. Reactive hyperplasia was present, the muscular fibers furnishing a rather dense stroma for the carcinoid cells. In the larger examples the submucosa, the muscularis propria and the peritoneum always demonstrated tumorous infiltration, sometimes in impressive degree. Pronounced myohypertrophy and fibrosis were present. This observation has been repeatedly confirmed but variously interpreted. The condition has been regarded by some as a "work hypertrophy" incident to the development of obstruction. However, evidence that local irritative phenomena were probably the operative factors was furnished by the case of Stewart, Willis and de Saram,[29] in which a small carcinoid tumor arose from the intestinal portion of an ovarian teratoma. Here the factor of obstruction was eliminated; yet these authors observed the usual myohypertrophy in zones of muscular invasion. Peritoneal spread in several of the tumors resulted in puckering and acute "kinking" of the intestine at that particular site. The importance of this feature in producing obstruction is attested by numerous cases in the literature; the frequent production of the phenomena by these "little carcinomas" has opened an avenue which may possibly lead to correct preoperative diagnosis of carcinoid tumors by means of roentgen rays.

Involvement of Nodes and Mesenteric Fat.—Involvement of regional lymphatic nodes constitutes the commonest criterion for attaching the designation "metastasizing" to a carcinoid tumor. Such involvement was present in 11 of the 13 cases in our series. Moreover, in contradistinction to assertions in the literature indicating that spread of carcinoid tumors is by direct extension [23] (and therefore not a true metastasis), in many of our cases there was true embolic metastasis by way of lymphatic channels. In short, it appeared from a study of these nodes that the spread thereto did not differ in any essential regard from that developed with "ordinary" carcinoma of the small intestine even to the actual incidence of such involvement.[30] In 37 per cent of our 30 cases and in 84.6 per cent of those in which metastases had occurred there was nodal metastasis. Invasion of mesenteric fat, like invasion of the nearby peritoneum, was observed in all 13 cases, but such involvement was not always apparent on gross inspection. Oftentimes the strands of tumor cells extended for only a short distance into this adipose connective tissue, and in several instances they did not reach as far as the regional lymphatic nodes. In 1 case multiple blocks of tissue were necessary for microscopic demonstration of mesenteric infiltration. No nodes had been found on this specimen, and yet the patient had succumbed as a result of metasasis two years after operation.

Involvement of Nerves.—The relation of nerves to the spread of carcinoid tumors has long been an interesting problem.[31] Masson [5] even went so far as to

29. Stewart, M. J.; Willis, R. A., and de Saram, G. S. W.: Argentaffin Carcinoma (Carcinoid Tumour) Arising in Ovarian Teratomas: A Report of Two Cases, J. Path. & Bact. **49**:207-212 (July) 1939.

30. Craig, W. McK.: Lymph Glands in Carcinoma of the Small Intestine: A Review of the Condition of the Glands in Carcinoma of the Gastro-Intestinal Tract, Surg., Gynec. & Obst **38**:479-485 (April) 1924.

31. (*a*) Humphries, E. M.: Carcinoid Tumors of the Small Intestine: A Report of Three Cases with Metastasis, Am. J. Cancer **22**:765-775 (Dec.) 1934. (*b*) Kross, I.: Carcinoid Tumors of the Small Intestine, Am. J. Digest. Dis. **6**:725-727 (Dec.) 1939. (*c*) Gáspár.[6d] (*d*) Bailey.[23]

state that the formation of a neuroma constitutes one stage in the development of an appendical carcinoid tumor. Investigators who have studied ileal carcinoid tumors, large and small, have been in universal agreement that no comparable neuromas are formed in this location. Many have observed hypertrophied nerves surrounded by carcinoid cells, however. In the present series actual invasion of nerves appeared to occupy a place secondary in importance to the phenomena of malignant infiltration of perineural lymphatic spaces. Such perineural involvement was found not only within the intestinal wall but to a lesser degree within the folds of the mesentery. The appearance at once recalled a similar observation made in connection with submaxillary adenocarcinomas of the cylindroma type.

Involvement of Blood Vessels.—Hepatic metastasis, in most cases of carcinoid tumor, supposedly stands as prima facie evidence of spread via the blood vessels. Although such a mode of dissemination has been considered as probable for a long time, actual demonstration has only occasionally [32] afforded proof of the process. In the present series actual invasion of veins by thrombi of tumor cells was observed in 5 of 13 cases. In 2 additional cases the presence of hepatic metastasis indicated such a mode of spread, but biopsy material was inadequate for purposes of microscopic confirmation. Moreover, we have observed the phenomenon of blood vascular invasion in some carcinoid tumors which apparently had not yet metastasized and which, according to some investigators, would therefore be classed as benign.

Involvement of Liver.—Metastatic carcinoid involvement of the hepatic parenchyma is considered by some investigators to be almost half as common as metastatic spread to regional nodes. Cooke [6b] found this ratio to be 4:5, and Ariel,[6a] reviewing the literature from 1930 to 1939, submitted a ratio of 1:3. In the present series, if one accepts as authentic the surgical findings at exploration, hepatic involvement was observed in 5 cases, as against 11 cases in which carcinoid deposits occurred in regional nodes.

Malignancy of Carcinoid Tumors.—Some investigators feel that appendical carcinoid tumors are benign and that all extra-appendical examples are malignant; others concede that all metastasizing carcinoid tumors are malignant, whereas those which fail to spread are benign [33] ; others again express the view that all carcinoid tumors, regardless of size and location and localization or extension, are malignant histologically and should be treated as "cancers." [34] In the case of small intestinal carcinoid tumors, moreover, the implications of malignancy are now being widely considered in the clinical as well as the pathologic sense. From the evidence afforded, by the study of this series and a comparison with examples of nonmetastasizing members of this group, appendical,[35] ileal and colonic, we contend that all carcinoid tumors are malignant neoplasms arising from glandular epithelium and therefore carcinomas in every sense of the word. It has been our constant observation that so-called benign and malignant examples are identical histologically, with cellular uniformity the keynote of microscopic diagnosis. Mitoses are practically never encountered. The tumor cells are derived from glandular (entodermal) elements and in the mucosal aspects of the tumors frequently reproduce glandular

32. Gáspár.[6d] Humphries.[31a]

33. Ewell, G. H., and Jackson, R. H.: Carcinoid Tumors of the Small Intestine, with Case Report (Multiple Benign Embryonal Carcinoid Tumors), Wisconsin M. J. **30**:737-740 (Sept.) 1931. Lewis.[9]

34. Willis, R. A.: Argentaffin Carcinomata ("Carcinoids") of the Small Intestine, M. J. Australia **2**:400-403 (Oct. 26) 1940. Ranson.[3] Gáspár.[6d]

35. Hopping, R. A.; Dockerty, M. B., and Masson, J. C.: Carcinoid Tumor of the Appendix, Arch. Surg. **45**:613-622 (Oct.) 1942.

spaces which occasionally contain droplets of mucus. Formation of acini sometimes is also observed in metastatic (nodal) deposits. The tumor cells, arising as they do through differentiation from granular cells of the intestinal crypts, produce these same granules, which may be specifically identified by means of appropriate stains.

Because of the aforementioned facts we submit that the designation grade 1 adenocarcinoma (carcinoid) should be appended to all tumors of this type. Such a designation would remind one at once of their malignant capacities combined with an expected slow evolution. It would also denote an origin from a specific cell type as distinguished from the "ordinary" type of adenocarcinoma, which is frequently of much higher grade (Broders) and consequently of more rapid growth and dissemination.[36]

SUMMARY

In a review of the records and pathologic specimens of 130 carcinomas of the small intestine, 30 so-called carcinoid tumors were encountered. Thirteen of these had metastasized locally or distantly. These 13 tumors affected persons in the older age groups and in 9 instances were responsible for disabling symptoms, chief among which were those indicative of chronic intestinal obstruction. Preoperative diagnosis of the type of lesion was not possible, but radical surgical procedures were carried out in the majority of cases, in accord with known results which had followed similar procedures used in dealing with carcinoid tumors. Fresh tissue identification of type was of considerable assistance in deciding this issue of treatments. Follow-up studies appeared to justify the type of treatment employed. Pathologically the neoplasms tended to be present in the terminal segments of the ileum as small orange submucosal nodules with minimal ulceration. In 50 per cent of the cases in which accurate information was available, the tumors were multicentric. There was pronounced infiltration of the submucosa, the muscularis, the peritoneum, the nerves, the lymphatic spaces and the blood vessels. Puckering and kinking in the region of tumor invasion were observed and may provide a valuable roentgenologic sign of identification. Involvement of regional nodes was observed in 11 and hepatic metastasis in 5 instances. Evidence was afforded on the basis of microscopic studies that all carcinoid tumors are in essence peculiar low grade (1, Broders) adenocarcinomas. It is suggested, however, that the word "carcinoid" be appended by virtue of customary usage and at the same time perhaps as a designation of the peculiar mode of origin, life history and spread of these rather unusual neoplasms.

The Mayo Clinic.

36. In 2 of our cases the simultaneous occurrence of the two types of adenocarcinoma was observed. This association has been noted recently by others (Warren, S., and Gates, O.: Multple Malignancy with Metastasizing Carcinoid of Ileum and Miliary Tuberculosis, Arch. Path. **18**:524-526 [Oct.] 1934. Humphries[31a]), who also observed that the simultaneous occurrence of tuberculosis and carcinoid tumors (Primrose, A.: Primary Carcinoma of the Small Intestine in an Octogenarian, Ann. Surg. **82**:429-435 [Sept.] 1925) appears to be on the decline.

AN OPERATION FOR SCAPHOCEPHALY

WALTER E. DANDY, M.D.
BALTIMORE

Acrocephaly and scaphocephaly are related deformities of the skull in infants and children. They are due to unexplained premature closure of the cranial sutures and result in crowding the brain within a space that is too small for its present size and its subsequent growth. As a result the eyeballs may (or may not) protrude and the child is listless and mentally backward and has headaches. Papilledema is frequently present, and there is convolutional atrophy of the skull and compression of the ventricular system. All the signs and symptoms are the result of general intracranial pressure.

Operative relief of these conditions has only recently been reported by King (1941),[1] although a preliminary report was made in 1937, when the operation was first performed. Two cases were reported, and in 1 at least a brilliant result was evident four and a half years later. The patient's condition had seemed hopeless and his physical appearance was frightful but a fine-looking boy appears in the later photographs. Woodhall [2] performed the same operation on 2 patients with fairly similar deformities and produced definite improvement over a period of two years. King's procedure consists in cutting into loosely lying fragments most of the vault of the skull on both sides, thus allowing the cranial chamber to expand before the fragments reunite. Woodhall aptly terms it the "morcellation" method of King. King does not open the dura; it would probably be dangerous to do so with the bony fragments lying loosely on it. Although the dura is a tough, inelastic membrane, it doubtless yields in time to the intracranial pressure, just as it expands with the normal growth of the brain.

The purpose of this communication is to present a different operative attack for the same conditions. Instead of breaking up the bone into fragments, I have enlarged the cranial chamber by lifting most of each side of the skull. Two operations with an interval of two to three weeks or months are performed.

OPERATION

A large longitudinal incision beginning at the hairline in front, extending to the occiput posteriorly and then curving downward and forward toward the ear is made about 2.5 cm. from the midline. The galea and skin are reflected and retracted forward. A bone flap equal in area to this exposure is cut away with a bone-cutting instrument, except over about a third of the longitudinal extent near the midline. The bone flap is elevated and broken at this uncut line, but the break is not complete; it leaves a hinge with good fixation. The bone is now raised about 3 cm. on this fixed hinge but is free elsewhere. The dura is opened parallel to the cut margin of the bone, except along the midline. The brain then promptly bulges to fill the space formed by the elevated bone. To fix the elevated bone flap a piece of bone is cut from the posterior margin of the flap and wired across the defect. After closure of the incision the head is encased in a light plaster cast.

1. King, J. E. J.: Oxycephaly, Tr. South. S. A. **54**:8, 1941.
2. Woodhall, B.: Oxycephaly, J. Pediat. **20**:585, 1942.

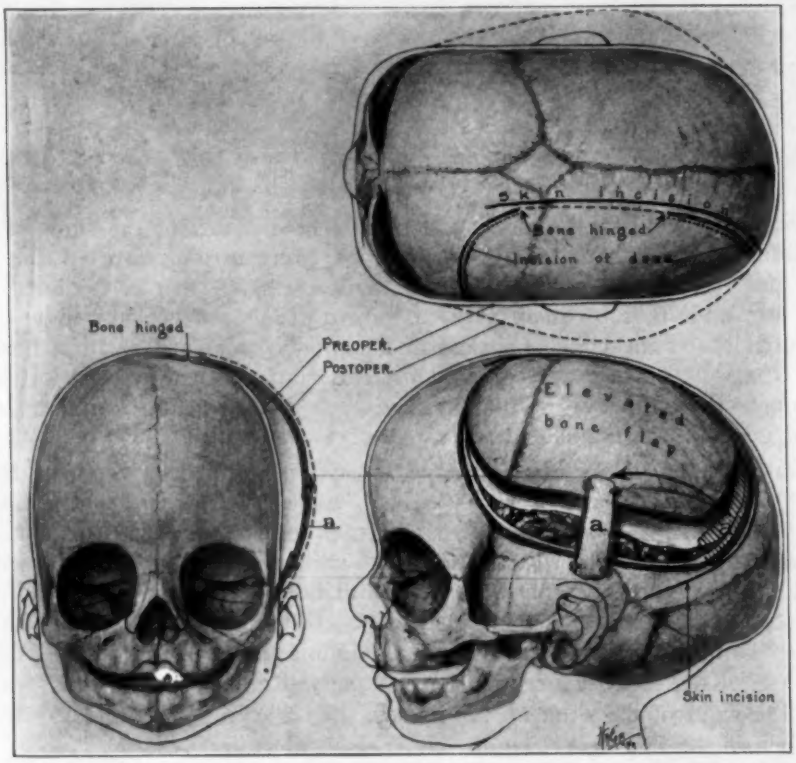

Fig. 1.—Drawing of the operative procedure for correction of scaphocephaly. The narrow head is enlarged by elevating a large bone flap on each side and holding it in position by a transplant of bone (from the bone flap). The dura is incised to allow the brain to expand. The same procedure is carried out on the opposite side two or three weeks later.

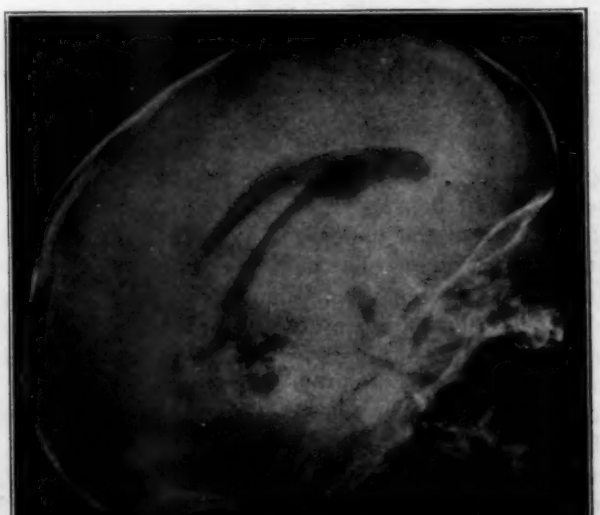

Fig. 2.—Ventriculogram showing the long, attenuated ventricles characteristic of scaphocephaly.

The time at which the second side is done can be determined individually. The purpose of the second operation is mainly to produce symmetry of the head, since the intracranial pressure is adequately controlled by the enormous bulge of brain afforded by the decompression of the first operation. In my case the baby was only 5 months old, and an interval of three months was allowed. At the first operation a thin celloidin plate was used and at the second an autotransplant of bone. The latter is probably preferable; it is easily obtained and the loss of bone is negligible. It is worthy of note that a ventricular injection of air was made before operation; the roentgenogram showed that the ventricles were attenuated and elongated to conform to the shape of the narrow scaphocephalic head.

Immediately after the first operation the child became alert, active and responsive and showed a remarkable change from the preoperative listlessness and rather stupid appearance. The baby has since developed normally, and ten months after the first operation is active, bright and seemingly normal in every way. The head is everywhere firm.

Fig. 3.—Photographs taken six months after the first operation showing front and top views of a patient treated by the method described in this article.

Although the long, narrow head of scaphocephaly is more easily transformed into a normally shaped head by this type of operation, than is the pointed, short head of acrocephaly, relief of cerebral symptoms should be secured equally well for either condition.

Whether or not incision of the dura with immediate decompression is essential I do not know. It does no harm and permits immediate filling of the large dead space that would otherwise be left between the dura and the elevated bone. Moreover, a long period must be required for the unopened dura to stretch enough to fill this large space.

My patient is much younger than those of King and of Woodhall. This is an advantage in that early relief of the cerebral compression doubtless prevents permanent stigmas. Then, too, the operative procedure is much simpler because the bone is so thin. It is preferable to operate on the right side first, because the major effects of the cerebral protrusion after the dura is opened are borne by the less actively functioning hemisphere.

SUPPURATIVE ANTERIOR MEDIASTINITIS IN AN INFANT FOLLOWING INTRASTERNAL BLOOD TRANSFUSION

OPERATION AND RECOVERY

LIEUTENANT MARK M. RAVITCH
MEDICAL CORPS, UNITED STATES ARMY

HISTORY OF INTRAMEDULLARY THERAPY

At least as far back as 1903 Wolff [1] practiced marrow puncture on laboratory animals, and in 1910 Ghedini [2] reported an experience of several years in obtaining specimens of bone marrow from 24 living human patients through puncture holes in the tibia. He recommended the method for the diagnosis of blood dyscrasias without pathognomonic alterations in the circulating blood and for the diagnosis of kala-azar. In 1923 Seyfarth,[3] who had been seeking a substitute for splenic puncture in the diagnosis of kala-azar, described his use of a small hand trephine and a platinum wire loop for obtaining specimens of sternal marrow with the patient under local anesthesia. His discovery foreshadowed the observations of Debré and his associates [4] that sternal puncture in man gives more frequent positive cultures for the diagnosis of septicemia than does venipuncture. In 1928 Sonnenfeld [5] described a very small trephine modifying Seyfarth's, and it was only a step from this to Arinkin's report [6] in 1929 of 180 aspirations of sternal marrow, a heavy lumbar puncture needle being used. Sternal puncture became at once a highly popular diagnostic method among hematologists, particularly abroad, and it was natural that the first use of the intramedullary route for administration of therapeutic agents should have been by hematologists. Josefson [7] in 1934 appears to have been the first of a number of investigators who injected liver preparations into the bone marrow of patients with pernicious anemia. Hoping for direct effect on the marrow, he made over fifty such injections and claimed good results. He used a sternal puncture needle with a collar and set screw as a depth guard and aspirated 4 to 5 cc. of marrow and injected 4 to 5 cc. of liver extract. He discussed the possible extension of the use of intramedullary injections: "Finally I should wish to say that if the intraossal method is and deserves to be accepted in the future

From the Departments of Surgery and Pediatrics, Johns Hopkins University School of Medicine, and the Harriet Lane Home of the Johns Hopkins Hospital.

1. Wolff, A.: Ueber eine Methode zur Untersuchung des lebenden Knochenmarks von Thieren und über das Bewegungsvermögen der Myelocyten, Deutsche med. Wchnschr. **29**:165, 1903.

2. Ghedini, G.: Neue Beiträge zur Diagnostik der Krankheiten der hämatopoetischen Organe mittels Probepunktion des Knochenmarks, Wien. klin. Wchnschr. **23**:1840, 1910.

3. Seyfarth, C.: Die Sternumtrepanation, eine einfache Methode zur diagnostischen Entnahme von Knochenmark bei Lebenden, Deutsche med. Wchnschr. **49**:180, 1923.

4. Debré, R.; Lamy, M.; Bonnet, H., and Broca, R.: La médulloculture, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1723, 1935.

5. Sonnenfeld, A.: Zur Technik der Sternalpunktion, Deutsche med. Wchnschr. **54**:1380, 1928.

6. Arinkin, M. I.: Die intravitale Untersuchungsmethodik des Knochenmarks, Folia haemat. **38**:233, 1929.

7. Josefson, A.: A New Method of Treatment: Intraossal Injections, Acta med. Scandinav. **81**:550, 1934.

we will perhaps be able to inject other remedies than campolon [liver extract] in the bone marrow. It is impossible to predict if the intraossal injection may then be preferred to the intravenous."

A mass of experimental work, chiefly that reported in the French literature, is concerned with intramedullary injections of every conceivable substance.[8] In the course of this work Benda [8f] studied the peculiarities of intramedullary injections. He determined that in the guinea pig intramedullary injections of drugs are equivalent to intravenous injections. Roentgenographic studies made with colloidal thorium dioxide showed instantaneous filling of the inferior vena cava and the lungs, and if a soluble iodide was used roentgenograms had to be taken while the injection was still in progress. Air embolism was as easily produced as by direct intravenous injection. Bacteria were as rapidly disseminated as when injected intravenously, and anaphylaxis could be induced as easily by intramedullary injections as by intravenous injections. These observations were confirmed by workers in other French laboratories. More recently the experiments have been repeated in this country.[9] Bernard [8h] in 1939 injected colchicine repeatedly into the sternal marrow of a 5 year old boy in a vain effort to affect his leukemia. In July 1940 Henning [10] reported a ten year experience with intrasternal injections of white blood cells for agranulocytosis. Roentgenograms taken with the aid of intrasternally injected iopax and other preparations showed immediate appearance of the material in the mammary veins. He reported the intrasternal administration of drugs, blood and fluids to human beings by means of a sternal puncture needle. For administration of blood, if the flow was too slow, he recommended the use of two needles. He expressed the opinion that his method was particularly adapted to the treatment of peripheral vascular failure with collapse of the peripheral veins. In November 1940 Morrison and Samwick [11] reported a single case of aplastic anemia with recovery after intrasternal administration of marrow. The present interest in the intrasternal and other intramedullary routes for administration of blood and fluids was aroused by the publications of Tocantins and O'Neill.[12]

---

8. (*a*) Torrey, J. C., and Kahn, M. C.: The Progressive Anemia Following a Single Intramarrow Injection of B. Welchii Toxins, Am. J. Path. **5**:117, 1929. (*b*) Bernard, J.: La stérilité des rats soumis aux injections intra-médullaires de goudron, Sang **9**:779, 1935. (*c*) Codvelle; Bernard, J., and Guichené: Aleucie hémorragique: Essai de traitement par les injections intra-médullaires de goudron, ibid. **10**:777, 1936. (*d*) Tosatti, E.: Lésions myélo-hématiques et stérilité provoquées chez le lapin par les injections intramédullaires de goudron, ibid. **10**:388, 1936. (*e*) Benda, R.: Renseignements fournsi par les injections intramédullaires de sang humaine chez le cobaye, ibid. **11**:659, 1937. (*f*) Benda, R.; Debray, C., and Bourée, J.: Injection du système veineux du cobaye par voie médullaire osseuse: Résultats qu'il est possible d'en attendre, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:662, 1937. (*g*) Bonnet, H.; Dreyfus, B., and Montefiore: Persistance comparée des microbes virulents inoculés au cobaye dans la moelle osseuse et dans le sang circulant, Compt. rend. Soc. de biol. **128**:485, 1938. (*h*) Bernard, J.: Leucémie aiguë: Essai de traitement par les injections intramédullaires de colchicine; modifications médullaires et sanguines, Sang **13**:434, 1939.

9 (*a*) Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids into the Circulation Via the Bone Marrow, Proc. Soc. Exper. Biol. & Med. **45**:782, 1940. (*b*) Tocantins, L. M.: Rapid Absorption of Substances Injected into the Bone Marrow, ibid. **45**:292, 1940.

10. Henning, N.: Die intrasternale Injektion und Transfusion als Ersatz für die intravenösen Methoden, Deutsche med. Wchnschr. **66**:737, 1940.

11. Morrison, M., and Samwick, A. A.: Intramedullary (Sternal) Transfusion of Human Bone Marrow: Preliminary Report, J. A. M. A. **115**:1708 (Nov. 16) 1940.

12. (*a*) Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids into the General Circulation via the Bone Marrow: Technique and Results, Surg., Gynec. & Obst. **73**:281, 1941. (*b*) Tocantins, L. M.; O'Neill, J. F., and Jones, H.: Infusions of Blood and Other Fluids Via the Bone Marrow: Application in Pediatrics, J. A. M. A. **117**:1229 (Oct. 11) 1941. (*c*) Tocantins and O'Neill.[9a] (*d*) Tocantins.[9b]

Intravenous therapy of all sorts, particularly the administration of fluids, blood and plasma, has come to play such a large part in present day therapeutics that the number, size and durability of a patient's veins may actually represent the difference between easy and adequate treatment on the one hand and difficult and inadequate treatment on the other. This observation is especially applicable in a long illness. For this reason the suggestion [13] that the marrow spaces of the sternum, femur and tibia be used for intravenous infusions seemed to present a solution to the problem of administration of fluids to patients "without veins."

The method has not yet been employed in either the surgical or the pediatric service of this hospital. Not more than 1 or 2 adult patients a year finally reach the point at which intravenous medication is all but impossible; and even for these it is usually possible by recourse to the jugular and the femoral veins to give enough fluid for several days until the more frequently employed superficial veins are once more usable as a consequence of resorption of extravasations, canalization of old thrombi or enlargement of collateral vessels. In the case of infants we have been struck by the fact that superficial veins are always available. Many articles, in journals and in textbooks of medicine and pediatrics, stress the importance of "cutting down" on the veins of infants for giving transfusions of blood. It is the practice in the pediatric service of the Johns Hopkins Hospital to resort to open venesection only for an infusion which is to run uninterruptedly for a number of days. The use of needles of fine bore (up to 27), with administration of the fluid under pressure, makes it possible to give all intravenous treatments, except the "continuous drip," by percutaneous puncture of superficial veins, even those as small as the digital veins of infants; not infrequently a fine needle, snugly taped in place, serves for continuous infusions. Despite the apparent advantages of a method which requires one to strike only the marrow cavity of a bone instead of the lumen of a fragile vein, we have not employed the infusion of fluids into the bone marrow, on the ground that it is an unnecessarily hazardous procedure, which is trying for the patient and which, on the basis of the figures supplied by the proponents of the method, will not deliver quantities of fluid with sufficient rapidity to justify its use.[14] The method requires special skill and experience, which are to be gained only from constant use, but its use without the special indications which exist only in occasional cases is not justifiable.

It is worth noting that in the case reported hereinafter, an intramedullary transfusion was attempted in one hospital, with serious consequences. Subsequently in the same hospital as well as in the Harriet Lane Home after the baby was transferred, although she was then edematous and almost moribund, no difficulty was encountered in giving blood and fluids at will by percutaneous puncture through veins of the scalp and the extremities. In fairness to Tocantins and O'Neill and other advocates of intramedullary transfusion, it must be pointed out that the statement that "in a child under 3 years of age, the marrow in the sternum is probably not developed to the point that it will allow this site to be used" [12a] was

13. Henning.[10] Tocantins and O'Neill.[13a] Tocantins, O'Neill and Jones.[12b] Tocantins, L. M.; O'Neill, J. F., and Price, A. H.: Infusions of Blood and Other Fluids Via the Bone Marrow in Traumatic Shock and Other Forms of Peripheral Circulatory Failure, Ann. Surg. **114**:1085, 1941.

14. The average rate of flow in the manubrium [12b] is 3.4 cc. a minute; in the body of the sternum, 3.1 cc. a minute, and in the tibia or femur of children, 1.7 cc. a minute. That is to say, according to these averages, it would require two and one-fourth hours to administer 500 cc. of blood to an adult; thus the use of intramedullary injections is precluded in an emergency unless the fluid is to be forced in by syringe. When this method was used a maximum rate of 57.5 cc. a minute was attained in 1 case.

disregarded. The special needle devised by Tocantins and O'Neill was not employed; but since sternal puncture is a familiar procedure and needles for its performance are in general use, one may expect, as reports are beginning to show,[15] that sternal puncture needles of varying design will be used for this new purpose. In the present instance, since there is nothing to indicate that the child had an infection of the blood stream before or after transfusion, the appearance of pus in the mediastinal extravasation suggests that the blood may have been contaminated. A few organisms introduced into a vein, and probably into the bone marrow, are ordinarily of no consequence.[16] In the mediastinum the results can be extremely serious. There is already one report in the literature[17] regarding the fatal effects of intrapleural administration of a large infusion of dextrose meant for the sternum. An autopsy was not done, and the status of the mediastinum was not known. The infusion was given during an elective operation, and death followed.

SUPPURATIVE ANTERIOR MEDIASTINITIS

Most discussions of mediastinitis deal with infections of the posterior mediastinum. Posterior mediastinitis results from esophageal or tracheal perforation, disease of the tracheobronchial lymph nodes, diseases of the lungs or the pleura, and extension from cervical infections. Furstenberg[18] has clearly demonstrated that the attachment of both the superficial fascia and the anterior layer of the pretracheal fascia to the under side of the manubrium prevents the spread of cervical infection into the anterior mediastinum. Nevertheless, Neuhoff and Jemerin[19] reported the case of a 9 month old infant who had an anterior mediastinal abscess in direct continuity with a cervical abscess. These authors reported a number of severe thoracic infections, usually associated with posterior mediastinitis, which finally involved the anterior mediastinum. However, these are exceptions. Cervical and posterior mediastinal infections rarely involve the anterior mediastinum, and anterior mediastinitis is in consequence an uncommon condition. A number of cases of alleged anterior mediastinal abscess in the literature are probably posterior mediastinal abscesses extending far anteriorly and displacing the soft tissues before them. Such a case is described by Neuhoff and Jemerin. A number of anterior mediastinal abscesses following simple fracture of the sternum have been described.[20] Acute hematogenous osteomyelitis of the sternum may cause acute suppurative anterior mediastinitis.[21]

The most important specific symptoms of acute suppurative anterior mediastinitis are edema of the head and arms with venous distention in the same region,

15. Gomez, E.; Collar, A., and Calderin, C.: Transmédula-ósea infusión, Rev. de med. y cir. Habana **47**:113, 1942.

16. However, Bonnet and his associates found in experimental septicemia that organisms remained in the blood stream eleven to fifteen days under their experimental conditions, but in the bone marrow twenty-one days. In the presence of trauma to the sternum, osteomyelitis might be expected to result in some cases.

17. Papper, E. M.: Bone Marrow Route for Injecting Fluids and Drugs into the General Circulation, Anesthesiology **3**:307, 1942.

18. Furstenberg, A. C.: Acute Mediastinal Suppuration, Tr. Am. Laryng., Rhin. & Otol. Soc. **35**:210, 1929.

19. Neuhoff, H., and Jemerin, E. C.: Acute Infections of the Mediastinum, Baltimore, Williams & Wilkins Company, 1943.

20. McKinlay, C. A.; Kinsella, T. J., and Radl, R. B.: Acute Essential Hypertension Precipitated by Mediastinal Abscess, Arch. Int. Med. **54**:645 (Oct.) 1934.

21. Perras, T.: Beitrag zur Chirurgie des Brustbeins und des Mittelfelles, Deutsche Ztschr. f. Chir. **254**:246, 1940.

and dyspnea. Lezius [22] made the point that in anterior mediastinitis the dyspnea is inspiratory and in posterior mediastinitis expiratory and that cyanosis is more apt to occur in the latter. Lezius as well as McKinlay, Kinsella and Radl [20] noted acute hypertension, which was also present in our patient. All authors agreed on the necessity for early resection of portions of the ribs or sternum or both.

REPORT OF A CASE

J. B., a Negro girl aged 8 months, was transferred to the Harriet Lane Home of the Johns Hopkins Hospital on Oct. 9, 1942, for surgical consultation because of complications following an intrasternal blood transfusion. Fever, dyspnea, edema of the face and arms and broadening of the mediastinal shadow were present. In May 1942, at the age of 3 months, she had been followed in the Harriet Lane Dispensary for one week because of acute nutritional disturbance, associated with otitis media and infection of the upper part of the respiratory tract. She was treated with sulfathiazole for five days, during which her temperature dropped from 104.2 to 98.6 F. and her symptoms subsided. The hemoglobin content of the blood was 10.5 Gm. per hundred cubic centimeters, and the white cell count was 5,000 to 8,000.

In July 1942, at the age of 5 months, the patient was admitted to the infants' ward of the Harriet Lane Home with a similar but more severe attack complicated by pneumonia in the upper lobe of the right lung. The hemoglobin content of the blood was 8.5 Gm. per hundred cubic centimeters. Nasopharyngeal cultures grew a type VII pneumococcus. Sulfathiazole therapy was started. Two days later the hemoglobin content of the blood was only 5.0 Gm. per hundred cubic centimeters. There was no sickling of the red blood cells. After three transfusions totaling 290 cc. of blood the hemoglobin content had risen to 12.0 Gm. She returned two weeks later with a history of diarrhea, fever and infection of the upper portion of the respiratory tract of five days' duration. This illness continued for three weeks. Pallor, cardiac enlargement, hepatomegaly and dyspnea developed, and she was admitted to another hospital, since no beds were available in the Harriet Lane Home. She stayed there for ten days and received 210 cc. of blood, which raised her hemoglobin content from 4.6 to 11.6 Gm. per hundred cubic centimeters.

On September 26 she returned to the Harriet Lane Home, with fever and vomiting. She was pale, and her heart was enlarged and was beating rapidly and overactively. The liver was palpable 1 fingerbreadth below the costal margin. The hemoglobin content of the blood was 4 Gm. per hundred cubic centimeters, and the red cells, as before, did not sickle. The wards in the Harriet Lane Home being full, she was again admitted to the other hospital.

On admission there she was described as being pale and listless. The skin was dry; there were no palpable glands; the tonsils were moderately enlarged, and the lungs were clear on auscultation and to percussion. The heart was moderately enlarged to the left, but the sounds were of good quality; the rate was rapid and the rhythm regular, and there were no murmurs. The liver was palpable 1 fingerbreadth below the costal margin; the spleen was not palpable. The urine was normal. The white cell count was 4,700 with 28 per cent polymorphonuclears and 72 per cent lymphocytes. The hemoglobin content was 4.8 Gm. per hundred cubic centimeters. Twenty cubic centimeters of whole blood was injected into one buttock.

On September 28 the hemoglobin content of the blood was 4.4 Gm. per hundred cubic centimeters and the red cell count was 1,040,000. The child was afebrile, but her condition was unchanged. On September 29 she was given intravenously 100 cc. of matched citrated blood which had been drawn on September 25. The bottle was recapped and placed in the ward's electric refrigerator. The transfusion was followed by a slight rise of temperature, but there was no chill. On September 30 the hemoglobin was 8.2 Gm.

On October 1 puncture of the sternal marrow was attempted, and marrow is said to have been obtained. The needle was described as a 16 gage sternal puncture needle. With the needle in place it was decided to administer blood intrasternally. Accordingly 75 cc. of the same blood which had been given on September 29 was given by gravity through the sternal puncture needle. After this the patient's temperature slowly rose to 104.0 F. and remained almost constantly at that level thereafter. It was noticed then that she was becoming progressively more edematous and that her face was disproportionately swollen. The liver remained palpably enlarged.

On October 2 the administration of mersalyl and theophylline produced slight reduction in the edema. On October 3 the hemoglobin content of the blood was 5.8 Gm. per hundred cubic

22. Lezius, A.: Die Behandlung der akuten eitrigen Mittelfellentzündung, Arch. f. klin. Chir. **196**:616, 1939.

centimeters. A transfusion of 60 cc. of blood into a vein of the scalp on October 6 was without incident.

On October 2 a roentgenogram of the heart (fig. 1*A*) showed that the cardiac shadow was enlarged, especially at the base. One on October 6 (fig. 1*B*) showed a considerable increase in the cardiac shadow which was much more pronounced over the base than in the area of the ventricles. The edema of the face became more striking, and the patient lay with her head thrown back. Sulfathiazole and digitalis, administration of which was started on October 6, had had no perceptible effect, and on October 9 the baby was transferred to the Harriet Lane Home for consideration of surgical intervention.

On admission her pulse was 180, her respirations 60 and her blood pressure 112 systolic and 84 diastolic. She was a well nourished infant, strikingly pale and with an extreme degree of facial edema. She appeared mortally ill. Dyspnea was severe. The head was held retracted, but the neck was not stiff. She had a spasmodic, paroxysmal, slightly brassy cough. The edema, which was most pronounced around the eyes and lips, extended to both upper extremities, and there was some pitting over the upper part of the thorax, particularly behind. There was a puncture wound over the center of the sternum, which was entirely covered with a bluish subcutaneous discoloration. The contour of the chest was peculiar, with an anteroposterior fulness.

She was seen by Dr. Helen B. Taussig, who made the following note: The heart seemed definitely enlarged. The retromanubrial dulness was increased and there was dulness over the

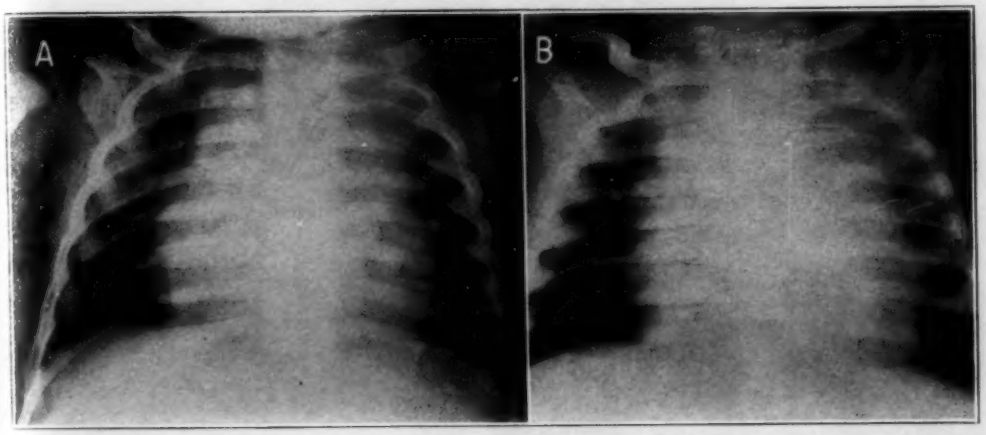

Fig. 1.—*A*, Oct. 2, 1942: enlargement of the cardiac shadow, particularly at the base. *B*, Oct. 6, 1942: increase in the mediastinal shadow.

left upper lobe continuous with it. The apex beat was felt in the anterior axillary line. The heart sounds were well heard and forceful in the axilla but were distant over the precordium itself. There was a striking discrepancy between the ease with which they were heard in the axilla and their muffled quality over the heart. There were no endocardial murmurs. The liver was slightly enlarged. Under the fluoroscope the heart shadows were hazy. The mediastinal shadow was wide, and it was difficult to make out the cardiac pulsation in the anteroposterior view. In the left anterior oblique position it was striking that there was a strong pulsation posteriorly in the region of the left ventricle and absence of pulsation anteriorly over the right ventricle, and that there was a wide mediastinal shadow which fused with the cardiac border and did not pulsate. In the right anterior oblique position the esophagogram was essentially normal, and in the anteroposterior position the esophagus seemed to deviate slightly to the left and then descended normally.

The red blood cell count was 1,670,000, the hemoglobin content 4.0 Gm. per hundred cubic centimeters and the white blood cell count 4,100, with 85 per cent lymphocytes. The nonprotein nitrogen content of the blood was 19 mg. per hundred cubic centimeters and the carbon dioxide-combining power was 64 volumes per cent. The total protein content was 5.2 Gm. per hundred cubic centimeters, the albumin content of the serum 3.1 Gm. and the globulin 2.1 Gm. The chloride content was 105 mg. per hundred cubic centimeters. The van den Bergh test showed 4.7 mg. of bilirubin per hundred cubic centimeters of serum.

There was by now general agreement that the patient presented the picture of obstruction to the superior vena cava due to the introduction of blood into the anterior mediastinum, where

under the fluoroscope a mass could be plainly seen. It was thought that the moderate hypoproteinemia which was present permitted the rapid appearance of edema.

There was some dispute as to whether there was merely a collection of blood, which could be trusted to resorb in time, or an actual abscess. This question was resolved by aspiration in the third interspace parasternally, which was the area of maximum dulness to percussion; with the needle angled toward the mediastinum the first puncture yielded 2 or 3 cc. of thick, reddish brown pus. Microscopic examination of the pus showed numerous fresh and partly autolyzed white blood cells and old, clumped red blood cells, some of which were in rouleau formation. Gram stain showed numerous polymorphonuclears and many gram-negative rods which proved on culture to be Escherichia coli.

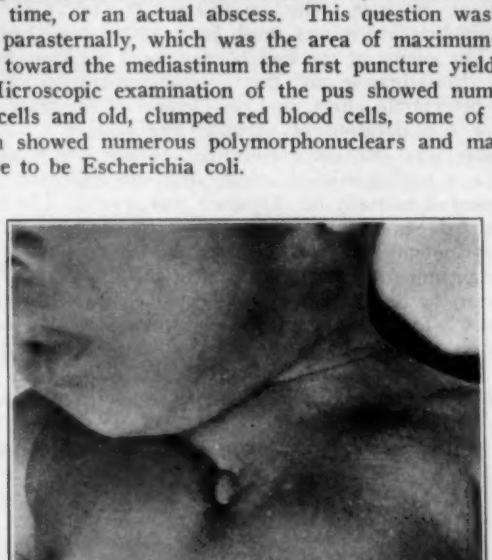

Fig. 2.—Nov. 30, 1942: small unhealed granulating wound.

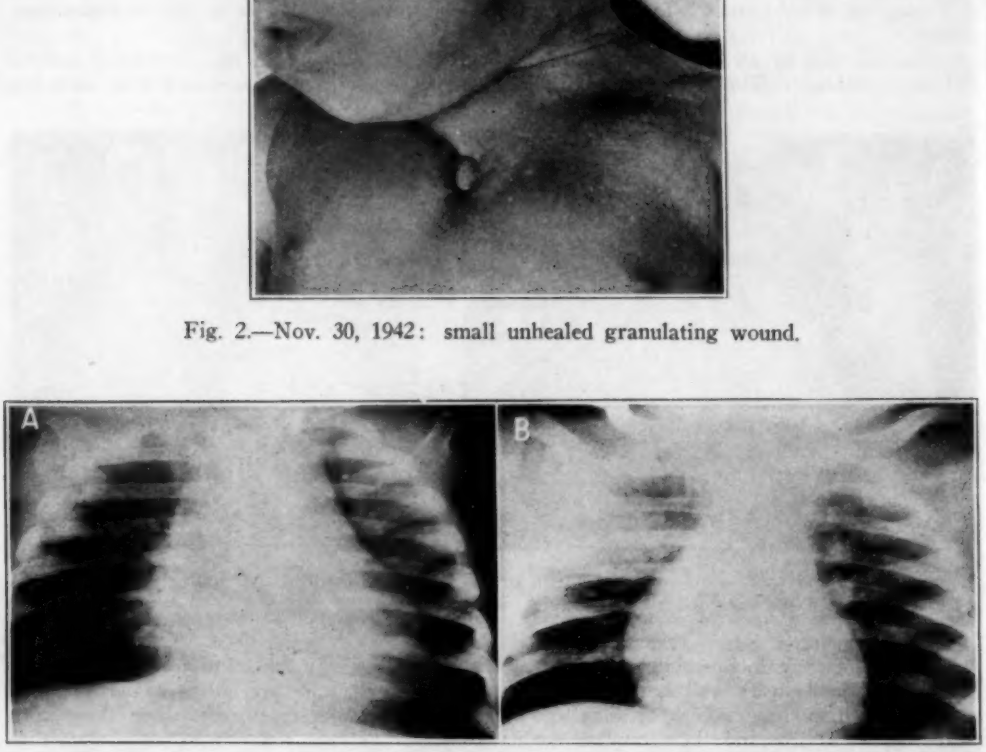

Fig. 3.—*A*, Nov. 18, 1942: some persistence of increase in the breadth of the mediastinal shadow as compared with *B*. *B*, July 19, 1942: narrower mediastinum at the time of the previous admission, when the patient had pneumonia.

Operation was undertaken on the day of admission with the patient under local anesthesia. A curved incision was made over the left side of the sternum and carried with difficulty through the edematous tissues down to the bone. At this point there was discharge of thin, dirty brown pus. The edge of the sternum and a neighboring costal cartilage, probably the third, were carefully rongeured away until a definite abscess cavity was exposed just behind the left border of the sternum and sufficiently large to admit one's index finger. The surrounding tissues were the seat of an intense cellulitis and exuded a dark brownish fluid; only in the small abscess cavity itself was there any thick, well formed pus, the fluid in the area involved by mediastinal cellulitis being thin. A little sulfanilamide powder was dusted into the wound, which was drained and lightly packed.

After operation the patient was given an intravenous transfusion of 100 cc. of blood, and treatment with sulfathiazole was begun. A continuous intravenous drip of blood was started

the next day, October 10, through which she received 145 cc. of blood, and on October 11, 200 cc. was given. On October 12 the edema of the face was greatly increased, she was unable to open her eyes and her hands and arms were edematous. The pulse was rapid and thready, and the temperature was still constantly elevated. Although the child had been lying with the head higher than the feet, no edema of the feet or ankles had developed.

On October 13 the edema began to subside, the pulse became stronger and slower and the temperature began to fall. The edema regressed slowly, so that it was almost gone by October 23 and completely gone by October 30. On admission her weight had been 7.04 Kg., but it dropped, with subsidence of edema, to 6.6 Kg. on October 14 and to 5.82 Kg. on October 21. Thereafter it slowly increased without recurrence of the edema. Administration of sulfathiazole was continued until November 7. At discharge, on November 30, she was afebrile, bright and cheerful, and the amount of hemoglobin in the blood was slowly rising without the aid of transfusions and had reached 10.0 Gm. per hundred cubic centimeters, with 3,270,000 red blood cells. The wound was all but healed (fig. 2). Comparison of roentgenograms taken two weeks before her discharge from the hospital (fig. 3*A*) with those taken during her previous admission, when she had pneumonia of the right upper lobe (fig. 3*B*), reveals some persistent widening of the mediastinum.

A final examination on April 30, 1943, revealed her to be well and vigorous. Her heart was not enlarged. Her blood pressure was consistently within normal limits (90 systolic and 60 diastolic). Under the fluoroscope the mediastinum was seen to be no longer widened and all cardiac pulsations were plainly visible.

SUMMARY

Suppurative mediastinitis in an infant of 8 months followed attempted intrasternal transfusion of blood through a needle inserted for the purpose of making a sternal puncture. The blood had been drawn six days previously and had been used two days before for an intravenous transfusion in the same child.

Fever, dyspnea and obstruction to the venous return from the head, chest and arms, manifested by pronounced edema, were the chief responses to the lesion. The head was held retracted and there was hypertension. Fluoroscopic examination showed a mass in the anterior mediastinum, overlying chiefly the base of the right ventricle.

Aspiration of the mediastinum yielded pus, and recovery followed resection of the overlying sternum and costal cartilage, with drainage of the abscess and of the diffuse mediastinitis.

THERAPY OF SHOCK IN EXPERIMENTAL ANIMALS WITH PLASMA AND SERUM PROTEIN SOLUTIONS

III. FREEZING SHOCK: CONCENTRATED PLASMA AND SERUM THERAPY WITH AND WITHOUT AMPUTATION OF THE DAMAGED EXTREMITY

LIEUTENANT (JG) ERNEST E. MUIRHEAD (MC), U.S.N.R.

LIEUTENANT (JG) LOUIS A. KREGEL (MC), U.S.N.R.

AND

JOSEPH M. HILL, M.D.

DALLAS, TEXAS

Freezing of one hindlimb of a dog has been demonstrated by studies carried out after thawing [1] to result in damage to the tissues and capillaries of the frozen site involving the skin, subcutaneous tissues and muscles down to the bones and leading to a lowered plasma volume and fatal shock. It was also observed that a greater portion of the loss in volume of the circulating plasma occurred during the first three hours after the freeze, at which time microscopic evidence of generalized visceral cellular damage and capillary dilatation (atony) was minimal or absent.[2] The interval between the third and the fourth hour was observed to be the borderline period beyond which generalized visceral capillary stasis and parenchymatous damage became pronounced.

When no therapy was instituted these animals [1] usually died in shock about eight hours after the freeze. In addition, it was observed [3] that a severe arterial hypotension occurred late, and that once this symptom appeared the complete reestablishment of the plasma volume delayed the onset of a fatal termination but did not avert it. It was therefore considered appropriate to study the effects of the following three therapeutic procedures conducted between three and three-tenths and four and eight-tenths hours after the freeze, during the borderline period of advanced generalized visceral changes.

Three groups of experiments with 10 dogs each were conducted. In the first group the damaged limb was amputated between three and two-tenths and three and nine-tenths hours (average) after the freeze was terminated, and no intravenous protein therapy was instituted. The second group received adequate intravenous protein therapy in concentrated form between four and two-tenths and four and nine-tenths hours (average), and the damaged limb was left intact. In the third group the damaged limb was amputated between three and three-tenths and three and ninety-nine hundredths hours and adequate intravenous protein therapy (concentrated) was instituted between four and three-tenths and four and eight-tenths hours (average).

From the William Buchanan Blood, Plasma and Serum Center and Department of Surgery, Baylor Hospital and College of Medicine.

1. Muirhead, E. E.; Ashworth, C. T.; Kregel, L. A., and Hill, J. M.: Experimental Freezing Shock: I. Changes in Body Fluids and Tissues, Arch. Surg. **45**:863-889 (Dec.) 1942.

2. The time element of three hours is related strictly to severe freeze of one hindlimb. Bilateral freezing considerably accelerated the depletion of plasma volume.

3. Muirhead, E. E.; Ashworth, C. T.; Kregel, L. A., and Hill, J. M.: The Therapy of Shock in Experimental Animals with Serum Protein Solutions: II. Fate in the Body of Concentrated and Dilute Serum and Saline Solutions, Surgery **14**:171-190 (Aug.) 1943.

METHODS

Healthy dogs were chosen, and before freezing was begun anesthesia was induced with pentobarbital sodium [4] in doses usually of 1 grain (0.06 Gm.) for every 5 pounds (2.3 Kg.) of body weight. The freezing procedure has been described.[1] The fur of one extremity was closely clipped, and care was taken to stop the freeze at the level of the inguinal ligament by padding the lower part of the abdomen and external genitalia with cloth and cotton and wrapping a rubber sheet around the dog over this insulating material. After the freeze the limb was allowed to thaw at room temperature. When the animals awakened, pain was relieved by appropriate doses of dilaudid given subcutaneously, but except for the original anesthesia the animals were kept just below the pain threshold. No analgesics were given beyond four hours postoperatively.

With proper surgical technic a guillotine type of amputation with disarticulation of the knee joint was performed. The sciatic nerve was severed first after the cutaneous incision, since tugging of this nerve precipitated extreme restlessness. Care was taken to keep bleeding at a minimum. After the amputation the wound was coated with sulfanilamide powder and the edges of the skin were approximated with interrupted mattress sutures. This procedure resulted in an oblique linear wound. Four preliminary amputations were performed to establish the technic, and subsequently experiments in various groups were alternated, starting with 2 dogs in group 3. The dogs in the latter group received plasma after the operation.

The batches of concentrated plasma and serum contained an average of 18.2 Gm. of proteins (albumin and globulin) per hundred cubic centimeters. These solutions were injected by means of 50 cc. syringes into the jugular vein. When the entire interval is taken for the injection the average rate was 0.2 cc. per minute per kilogram of body weight (average of 100 cc. given in forty minutes to dogs weighing an average of 12 Kg.). We wish to stress, however, that the doses were injected intermittently. Usually 5 to 10 cc. was injected in ten to thirty seconds, with an interval of one and five-tenths to two minutes between doses. On occasions the injections were made at slower rates, as will be explained hereinafter. In these experiments the intervals between injections were chosen for a dual purpose. Time was allowed for the excess sodium citrate in the plasma to be oxidized, its transient binding effect on the calcium in the circulating plasma being considerably reduced. Time was also allowed for accommodation of the circulatory system to the effects of the concentrated solutions, including a sudden increase in plasma volume resulting from the transfer of tissue fluids into the blood stream and the increase in the venous return to the heart of red blood cells.[8]

A sample from each injected dose of concentrated plasma and serum was taken for a protein determination in order that the exact number of grams of protein given each animal could be determined. The doses of protein given had been previously observed [3] to effect an adequate replacement of the plasma volume and circulating proteins for dogs of this size.

Human plasma and serum [5] prepared by the pooling of bloods technic [6] were used. The plasma was obtained from citrated blood and was desiccated by the adtevac process.[7] Usually

---

4. The pentobarbital sodium was furnished by Abbott Laboratories, North Chicago, Ill.

5. Before the present experiments we had not observed reactions to agglutinin-free human plasma in dogs other than reactions attributable to citrate, i. e., transient tetany, and reactions discussed later in the text as "transient depressor effect." Urticaria has been observed by others (Ashworth, C. T.: Unpublished data), but we did not encounter it in these experiments. During a more recent group of experiments [16] on dogs occasional changes in blood pressure of anaphylactoid type were observed following small doses of normal or concentrated human plasma. Only a few dogs responded in this manner, and no anaphylactoid fatalities have been encountered. The arterial pressure dropped gradually to levels around 50 mm. of mercury and returned to normal within twenty to forty minutes. When the recovery occurred, doses of the same batch of plasma similar to the original one or larger failed to initiate a similar depressor effect. These anaphylactoid manifestations were altogether different from the depressor effect referred to later. The fact that all animals in group 3 completely recovered, while those in group 2 died in shock, seems to support the deduction that anaphylactoid phenomena did not influence the present results.

6. Hill, J. M., and Muirhead, E. E.: Desiccated Plasma for National Defense: Mass Production Methods Based on the Adtevac Process, J. Lab. & Clin. Med. **27**:812-819 (March) 1942.

7. Hill, J. M., and Pfeiffer, D. C.: A New and Economical Desiccating Process Suitable for the Preparation of Concentrated Plasma or Serum for Intravenous Use: The Adtevac Process, Ann. Int. Med. **14**:201-214 (Aug.) 1940.

15 Gm. of the dry product was dissolved in 45 cc. of solvent (water and dilute citric acid solution).

Samples of venous blood were collected from an exposed jugular vein without hemostasis for duplicate determinations of the hemoglobin concentration (Sanford-Sheard photoelectric method [8]) and the plasma protein concentration (Greenberg method [9]). The mean carotid arterial pressure was taken with a mercury manometer with 2.5 per cent sodium citrate solution in the system. The control procedures were performed before the freeze and immediately after the onset of pentobarbital sodium anesthesia.

The wounds in the neck exposing the carotid artery and jugular vein were closed after the application of sulfanilamide powder.

The animals were kept at room temperature. Those which survived were allowed to drink water ad libitum fourteen to sixteen hours after the operation. The subsequent diet consisted of dog biscuits and ground meat.

Autopsies were performed on 21 animals (7 from each group), and representative samples of tissue were obtained from the viscera, the thawed limb, the amputation site and the remote somatic musculature for microscopic study with the routine hematoxylin-eosin stain. This procedure was conducted shortly after death. The protein concentration of the edema fluid in the thawed limb was determined in 7 animals.

RESULTS

All of the 30 animals in the three groups displayed a degree of venous hemoconcentration after three to four and two-tenths hours which according to previous studies [1] accounted for 75 to 85 per cent of the loss in plasma volume necessary to produce fatal shock by this procedure (severe freeze). The average plasma protein concentration during this period was slightly increased, partly as a result of hemoglobinemia. The mean arterial pressure either was slightly elevated or remained unchanged.

All of the observations up to this time (three to four and two-tenths hours) corroborated previous studies.[1] Since a similar procedure (severe freeze) was previously observed always to end fatally, any success in averting a fatal outcome is taken to be the result of the therapeutic measures instituted. With this reasoning in mind the results will be analyzed.

I. AMPUTATION; NO PROTEIN THERAPY (TABLE 1)

Five of the 10 animals died within twelve hours after the amputation. The appearance of the tissues was the same as that found after death from shock without amputation. Three dogs died one to two weeks later in a state of extreme anemia and hypoproteinemia without evidence of gross hemorrhage from the operative site. Two dogs lived and subsequently appeared healthy.

The average mean arterial pressure fifty-four minutes after the operation was 18 mm. of mercury lower than the control level. No instance of severe hypotension was encountered up to this time. The venous hemoglobin was usually slightly lowered after the operation. The plasma protein concentration was lowered by an average of 0.62 Gm. per hundred cubic centimeters. These changes probably resulted from loss of blood during the operation.

The histopathologic findings for each group are discussed under a separate heading below.

II. PROTEIN THERAPY; NO AMPUTATION (TABLE 2)

Eight of the 10 animals died twelve to twenty hours after the concentrated protein therapy. The appearance of the tissues was likewise that observed in

8. Sanford, A. H., and Sheard, C.: The Determination of Hemoglobin with the Photoelectrometer, J. Lab. & Clin. Med. **15**:483-489 (Jan.) 1930.

9. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, J. Biol. Chem. **82**:545-550 (May) 1929.

animals dying in shock. The limb which had been frozen and thawed was found to be markedly swollen, much larger than in animals who had died in shock without therapy.[1] The edema was present throughout the limb but was most pronounced in the subcutaneous region.

Two animals died seven and nine days later after remaining drowsy and stuporous and displaying a recurrence of hemoconcentration. The damaged limb was gangrenous and infected.

The mean arterial pressure at the time of therapy (average four and two-tenths hours after the freeze) was in the normal range (average 152.4) and after

TABLE 1.—*Amputation—No Protein Therapy*

Dog	Weight, Kg.	Time of Amputation, Hours After Termination of Freezing	Interval	Blood Pressure, Mm. of Mercury	Venous Hemoglobin, Gm. per 100 Cc.	Plasma Protein Concentration, Gm. per 100 Cc.	Comments
1	13	3.5-4.5	Control	155	14.45	....	Died within 10 to 12 hr.
			2.75 hr	170	20.0		
			20 min. after operation	125	19.9		
2	14.5	3.1-4.25	Control	173	13.85	6.96	Lived 2 mo.; killed; hemoglobin, 15.85, 14.7, 12.95; serum protein, 6.16, 6.12, 7.16
			2.75 hr	158	19.65	7.68	
			40 min. after operation	155	19.15	6.24	
3	12.5	3.3-4.3	Control	158	12.0	6.9	Died in 4 hr.
			3.1 hr	170	17.0	7.2	
			1.1 hr. after operation	120	16.4	7.28	
4	17.1	3.1-4.1	Control	135	14.45	7.36	Died within 10 to 12 hr.
			3 hr	160	19.15	7.72	
			1.1 hr. after operation	143	19.4	7.2	
5	11.3	3.1-3.75	Control	158	15.0	6.72	Died 14 days later with anemia, hypoproteinemia *
			3 hr	165	19.7	7.28	
			2.25 hr. after operation	135	19.15	7.22	
6	9	3.2-3.75	Control	160	12.95	5.56	Died 8 days later with anemia, hypoproteinemia *
			3.1 hr	120	17.0	7.16	
			10 min. after operation	95	16.2	5.9	
7	7.1	3.1-3.3	Control	148	10.4	....	Died within 10 to 12 hr.
			3 hr	135	17.15	7.92	
			1.1 hr. after operation	102	16.7	7.08	
8	98	3.5-3.9	Control	158	13.25	6.4	Died within 10 to 12 hr.
			3.3 hr	165	19.0	7.12	
			18 min. after operation	142	19.15	6.85	
9	6	3.2-3.6	Control	105	12.65	5.64	Lived
			3.1 hr	130	17.5	6.04	
			1.1 hr. after operation	105	16.5	5.26	
10	9.8	3.5-3.9	Control	130	12.3	6.16	Died 10 days later with bronchopneumonia and shock picture
			3.5 hr	160	17.15	6.4	
			32 min. after operation	102	16.65	6.0	
Average	11	3.26-3.93	Control	148	13.13	6.46	5 dogs died in shock; 3 dogs died 8 to 14 days later with anemia and hypoproteinemia; 2 dogs lived
			3 hr	153.3	18.33	7.18	
			54 min. after operation	122.3	17.92	6.56	

* Hemoglobin level 3.4 and 3.7 Gm. per hundred cubic centimeters; plasma protein concentration 4.1 and 4.4 Gm. per hundred cubic centimeters.

therapy (average thirty-six minutes) fell slightly (average 142.8). The plasma protein concentration of the recipient was lowered after therapy by an average of 0.33 Gm. per hundred cubic centimeters. Since a concentrated protein solution of three to three and five-tenths times normal concentration was given, the lack of elevation of the concentration of protein in the recipient's circulating plasma is interpreted as indicating the entrance of fluid into it. This reasoning is further supported by the lowering of the concentration of hemoglobin in the venous blood. The latter was not lowered to the control level as one would expect it to be after an adequate replacement of the plasma volume. This feature has been observed previously[3] and will be discussed later.

III. AMPUTATION; PROTEIN THERAPY (TABLE 3)

All of the 10 animals lived and appeared healthy subsequently. These animals were killed an average of twenty-eight days after the operation. Postmortem examination revealed no abnormality of the viscera.

The day after the operation half of the animals displayed a decrease in venous hemoglobin of 1.0 to 2.5 Gm. per hundred cubic centimeters below the control

TABLE 2.—*Protein Therapy—No Amputation*

Dog	Weight, Kg.	Time of Therapy, Hours After Termination of Freezing	Interval	Blood Pressure, Mm. of Mercury	Venous Hemoglobin, Gm. per 100 Cc.	Plasma Protein Concentration, Gm. per 100 Cc.	Comments
1	14.3	4.3-5	Control 4.2 hr. 30 min. after therapy	158 105 120	13.85 19.9 18.15	5.8 8.16 7.72	Concentrated human plasma, 87 cc. = 19.7 Gm. protein; died within 12 hr.
2	13.7	4.6-5.3	Control 4.6 hr. 38 min. after therapy	162 200 165	14.15 21.65 19.7	5.73 6.96 6.56	Concentrated human plasma, 119 cc. = 21.8 Gm. protein; died within 12 hr.
3	11.5	4.3-5	Control 4.3 hr. 35 min. after therapy	140 150 100	13.85 18.65 15.55	5.64 6.24 5.92	Concentrated human plasma, 99 cc. = 18 Gm. protein; died within 12 hr.
4	....	4-4.5	Control 4 hr. 33 min. after therapy	112 132 135	11.3 18.15 15.8	4.82 6.0 6.12	Concentrated human plasma, 131 cc. = 21 Gm. protein; died within 12 hr.
5	10.6	4-4.5	Control 4 hr. 1.1 hr. after therapy	143 145 132	13.4 23.0 20.65	.... 7.32 7.28	Concentrated human plasma, 101 cc. = 18.5 Gm. protein; died within 20 hr.
6	15	4-4.8	Control 4 hr. 53 min. after therapy	175 155 154	13.25 22.7 21.15	.... 8.0 6.52	Concentrated human plasma, 109 cc. = 19.5 Gm. protein; died within 18 hr.
7	19.4	4.8-5.4	Control 4.8 hr. 16 min. after therapy	175 125 135	12.65 18.15 14.7	7.2 7.68 7.2	Concentrated human plasma, 115 cc. = 19.7 Gm. protein; next day hemoglobin, 17.15; protein, 7.28; died 7 days after therapy
8	13.6	4-4.7	Control 4 hr. 42 min. after therapy	165 200 190	13.85 19.4 15.85	5.56 6.48 6.52	Concentrated human plasma, 112 cc. = 19.1 Gm. protein; died within 12 hr.
9	10.7	4-5	Control 4 hr. 31 min. after therapy	152 160 152	13.85 21.0 18.4	5.64 6.56 6.43	Concentrated human plasma, 110 cc. = 17.9 Gm. protein; died within 12 hr.
10	17	4-4.7	Control 4 hr. 15 min. after therapy	165 152 145	15.55 21.3 19.1	6.14 6.8 6.6	Concentrated human plasma and canine serum; 126 cc. = 21.3 Gm. protein; died 9 days later
Average	13.97	4.2-4.89	Control 4.19 hr. 36.3 min. after therapy	154.7 152.4 142.8	13.57 20.39 17.9	5.81 7.01 6.68	Concentrated human plasma, 110.9 cc. = 19.6 Gm. protein; 8 died in shock; 2 died 7 to 9 days later from gangrene and shock

level and in the other animals the venous hemoglobin was almost the same as the control level. In 4 animals the concentration of protein in the plasma was lowered by an average of 1.0 Gm. per hundred cubic centimeters the day after the operation. At the time the animals were killed, the plasma protein concentration was near or slightly above the control level and the hemoglobin concentration was slightly below the control.

The surgical wound healed well. The upper three fourths of the wound healed by primary intention. Usually the lower fourth, opposite the protuberance by

the ischium, dehisced and healed by means of a granulating surface. Occasionally a small zone of infection developed in the skin, but these areas were readily controlled. No instance of complete wound dehiscence or of widespread infection was observed.

Usually a slight decrease in the venous hemoglobin concentration and plasma protein concentration occurred after the operation and prior to plasma therapy.

TABLE 3.—*Amputation and Protein Therapy*

Dog	Weight, Kg.	Time of Amputation, Hours After Termination of Freezing	Time of Therapy, Hours After Termination of Freezing	Interval	Blood Pressure, Mm. of Mercury	Venous Hemoglobin, Gm. per 100 Cc.	Plasma Protein Concentration, Gm. per 100 Cc.	Comments
1	7.2	2.9-3.6	4-4.5	Control	130	10.4	....	Concentrated human serum, 95 cc. = 16.5 Gm. protein; lived
				2.9 hr	120	15.3	....	
				4 hr	95	14.45	....	
				14 min. after therapy	130	9.5	....	
2	10.3	3-4	4.23-4.8	Control	130	13.7	....	Concentrated human serum, 90 cc. = 16.4 Gm. protein; lived
				3 hr	140	20.0	....	
				4.1 hr	125	20.15	....	
				48 min. after therapy	125	15.0	....	
3	11	3.1-4	4.25-4.83	Control	135	13.25	6.48	Concentrated human serum, 76 cc. = 14.3 Gm. protein; lived
				3 hr	160	20.65	6.2	
				4.1 hr	130	19.5	7.2	
				33 min. after therapy	125	15.4	6.9	
4	12.5	3.3-4.3	4.35-5	Control	158	14.8	7.28	Concentrated human plasma, 83 cc. = 17.4 Gm. protein; lived
				3.1 hr	150	22.15	7.24	
				4.3 hr	118	21.9	6.94	
				30 min. after therapy	134	18.5	7.04	
5	9.1	3.1-3.9	4.5-5.1	Control	140	16.5	7.04	Concentrated human plasma, 83 cc. = 17.7 Gm. protein; lived
				3.1 hr	168	20.9	7.58	
				4.5 hr	125	20.15	....	
				15 min. after therapy	140	16.1	8.42	
6	15	3.5-4.5	5-5.3	Control	145	13.25	5.76	Concentrated human plasma, 110 cc. = 19.7 Gm. protein; lived
				3.5 hr	165	19.0	6.72	
				4.5 hr	130	19.15	6.0	
				32 min. after therapy	130	14.15	7.22	
7	8.8	3.3-3.75	4-4.3	Control	160	15.0	....	Concentrated human plasma, 113 cc.; lived
				3.3 hr	175	19.65		
				3.75 hr	160	20.15		
				1 hr. after therapy	180	13.8		
8	10	4-4.5	4.75-5.3	Control	140	13.85	6.44	Concentrated human plasma, 111 cc. = 21.2 Gm. protein; lived
				4 hr	155	22.0	6.72	
				4.75 hr	130	21.65	6.44	
				17 min. after therapy	142	15.0	7.04	
9	6.36	3.3-3.5	3.75-4.6	Control	148	14.15	5.6	Concentrated human plasma, 86 cc. = 16.9 Gm. protein; lived
				3.3 hr	150	18.15	6.24	
				3.75 hr	105	18.15	5.76	
				38 min. after therapy	160	13.85	6.72	
10	10.45	3.5-3.9	4.3-4.9	Control	155	11.4	5.76	Concentrated human plasma, 115 cc. = 21.1 Gm. protein; lived
				3.5 hr	130			
				4.3 hr	135	18.65	6.48	
				28 min. after therapy	145	10.9	6.4	
Aver.	10.0	3.3-3.99	4.3-4.86	Control	144.1	13.6	6.32	Concentrated human serum and plasma, 96.2 cc. = 17.9 Gm. protein; all lived
				3.27 hr	151.3	19.7	6.78	
				4.2 hr	125.3	19.4	6.47	
				31.5 min. after therapy	141.1	14.2	6.96	

An average of thirty-one and five-tenths minutes after therapy with concentrated plasma (citrated) there was an increase in plasma protein concentration of only 0.49 Gm. per hundred cubic centimeters. This feature is once more taken to indicate a shift of fluid into the plasma stream. Again it was observed that the venous hemoglobin was usually not lowered to the control level in intervals up to thirty minutes after therapy.

HISTOPATHOLOGIC STUDIES

The appearance of various tissues in the late phases of this type of shock has been described.[1] The changes may be placed in three subdivisions: (1) vascular changes (mostly capillary and venous dilatation with packing of the red blood

cells); (2) interstitial changes (such as edema, capillary hemorrhages and leukocytic infiltration), and (3) parenchymatous changes (acute parenchymatous degeneration, fatty degeneration, atrophy, necrosis and necrobiosis involving mostly the liver, the kidneys and the adrenal cortex).

It seems noteworthy that the appearance of the tissues of the animals that died in group 1 (amputation; no protein therapy) and in group 2 (no amputation; protein therapy) was decidedly similar. The animals in group 1 that lived seven to fourteen days were included. In the latter group 1 animal (dog 10) had massive pulmonary edema with superimposed focal bronchopneumonia. All of these animals displayed capillariovenous stasis of the lungs, the myocardium, the

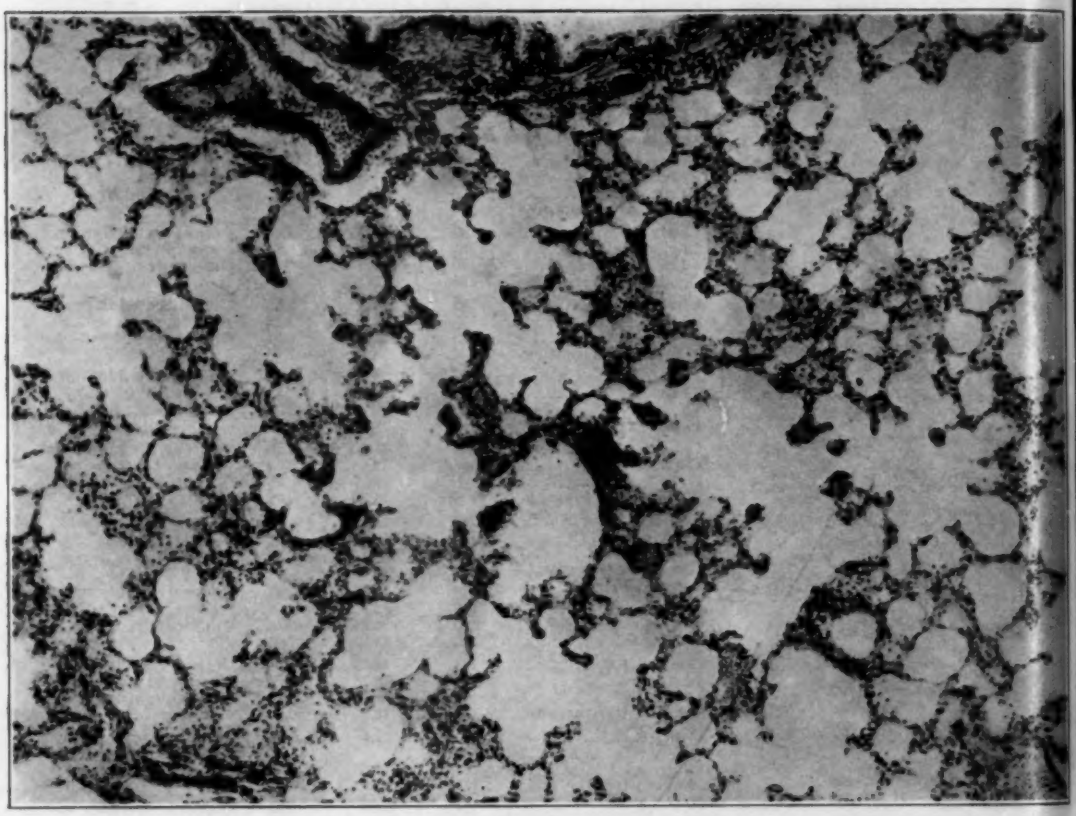

Fig. 1.—Dog 6, group 3 (amputation; protein therapy); lived; photomicrograph of a lung showing normal microscopic appearance. This animal was killed twenty-five days after the operation. See table 3 for other details.

liver, the kidneys and the adrenal cortex, pulmonary edema and small pulmonary hemorrhages, prominent atrophy of the hepatic cords (central) and the adrenal cortex, polymorphonuclear neutrophilic infiltration of the adrenal cortex and parenchymatous degeneration of the convoluted renal tubules. In addition, there was frequent central necrosis of the lobules of the liver and occasional focal necrosis of the renal tubules and the adrenal cortex. Precipitated protein material in the capsular space of the renal corpuscle and focal hyaline casts in the medullary tubules of the kidney were frequently observed. The spleen was firmly contracted and almost bloodless. Capillary dilatation of the intestinal mucosa was not as consistently observed as previously. Random samples of the somatic musculature

revealed only scattered dilated capillaries, and most of the muscle bundles had closely arranged fibers with collapsed intervening capillaries.

The parenchymatous lesions of the liver were more pronounced than in those observed in previous studies.[1] Two significant observations were made: First, the hepatic cords near the central vein were thin and narrow, so that the cells appeared elongated and the sinusoids widened. Second, there were frequent foci of coagulative necrosis, particularly near the central zones. In the latter areas the nuclear substance had disappeared. In 3 livers the necrosis involved over 50 per cent of the parenchyma in the sections examined, and there was confluence of several necrotic zones. Fatty degeneration was well advanced in 1 liver. The

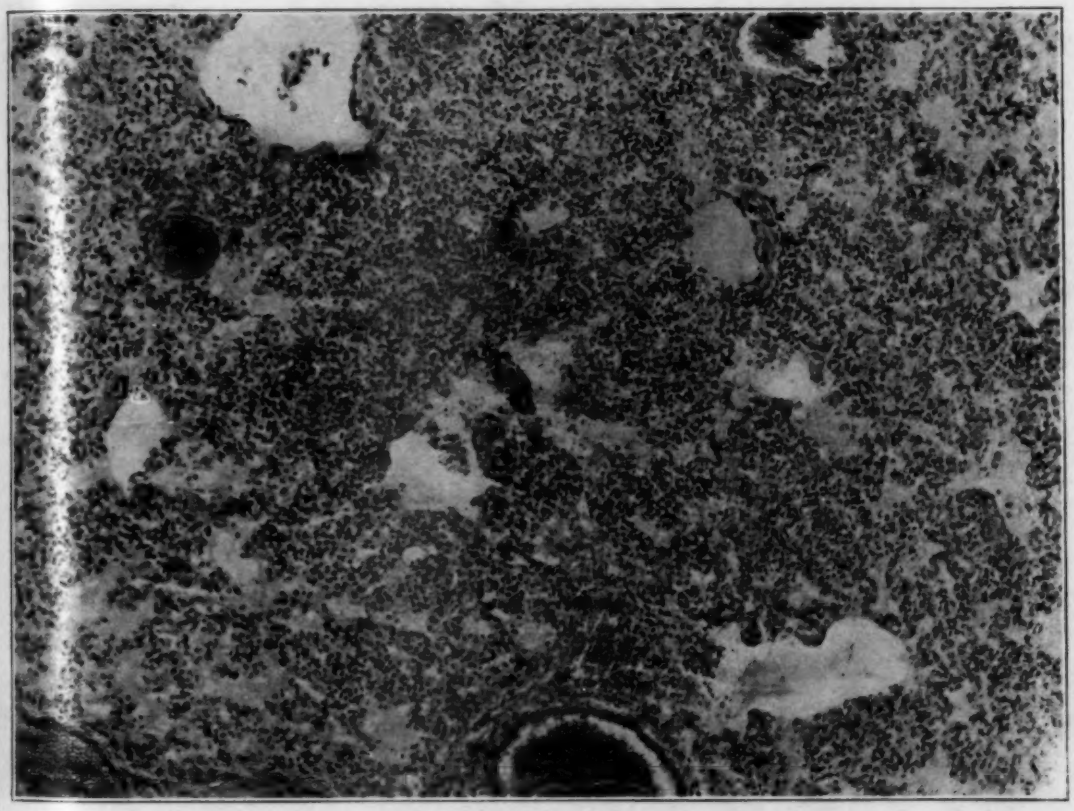

Fig. 2.—Dog 9, group 2 (protein therapy; no amputation); died in shock; photomicrograph of a lung showing pulmonary edema, capillariovenous congestion and capillary hemorrhages.

changes were more prominent in group 2 than in group 1. The dogs in the former group lived longer than those in the latter.

The hepatic lesions were similar to two types of lesions (central atrophy and central necrosis) described by Lambert and Allison [10] in 1916 in relation to passive hyperemia of the liver associated with backward heart failure. Moon [11] has commented on the close similarity of the appearance of the viscera in shock and in generalized passive congestion, a feature borne out by these hepatic lesions.

10. Lambert, R. A., and Allison, B. R.: Types of Lesions in Chronic Passive Congestion of the Liver, Bull. Johns Hopkins Hosp. **27**:350-356 (Dec.) 1916.

11. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

The cells of the adrenal cortex (mainly zona fasciculata) in both group 1 and group 2 displayed a diffuse decrease in lipid content. There was loss of the normal foamy appearance, and the cytoplasm of the cells appeared narrow and dense and was partaking heavily of the eosin stain. Thus the cells of the zona fasciculata resembled the cells of the zona reticularis. Occasionally isolated areas of the zona fasciculata had cells that were indistinct and were seemingly undergoing a gradual necrosis or wasting away (necrobiosis). Patchy capillary hyperemia of the zona fasciculata and circumferential hyperemia of the zona reticularis were observed. As in previous studies, prominent infiltration of the cortex by neutrophilic leukocytes was frequently observed.

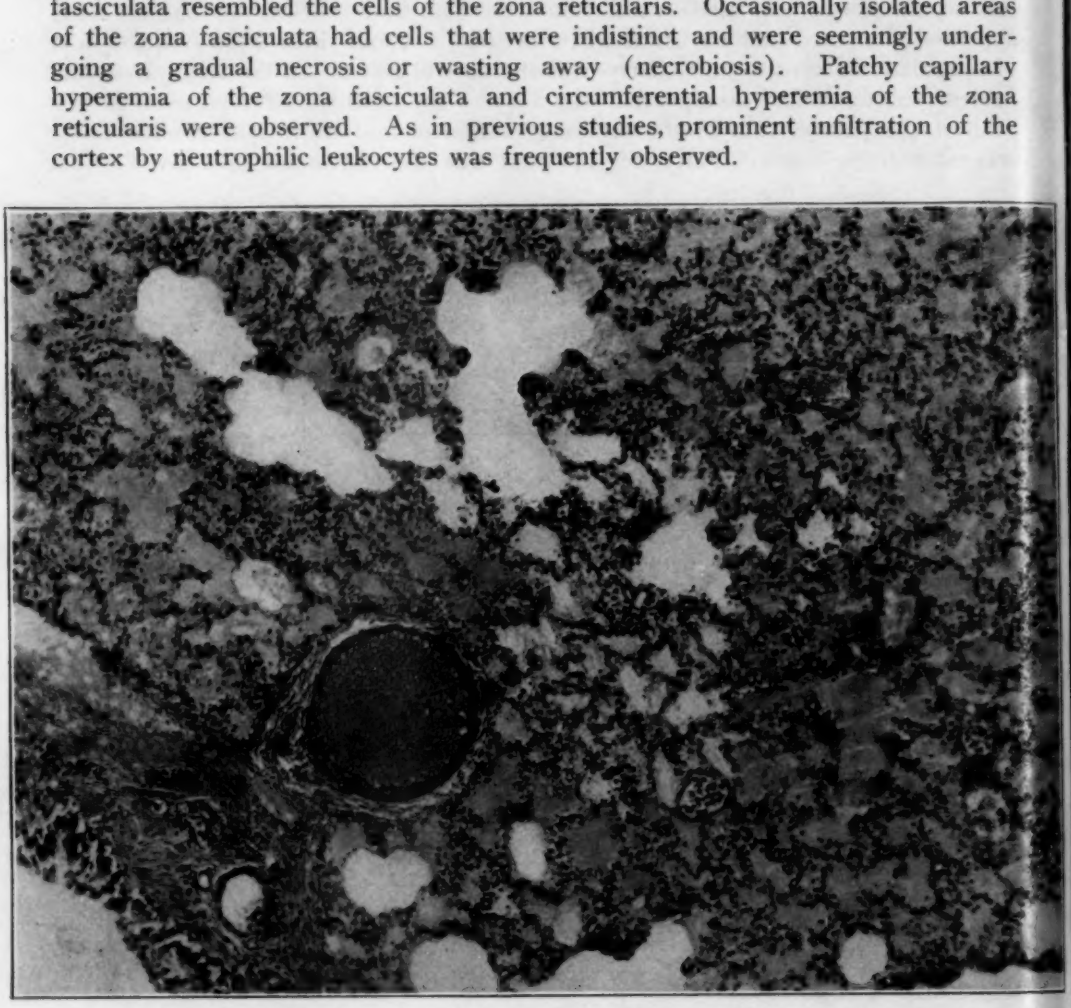

Fig. 3.—Dog 10, group 1 (amputation; no protein therapy); died ten days later; photomicrograph of a lung showing pulmonary edema, capillariovenous congestion and capillary hemorrhages.

Tissues from all of the animals in group 3 (amputation; protein therapy) were normal both grossly and microscopically. Tissues from dog 2 of group 1 were likewise normal. The livers of these animals had the usual lighter staining central areas and darker periphery observed in normal livers. The adrenal cortex was filled with lipid. There was no capillariovenous stasis, even in the region of the amputation. The scar of the amputation wound was dense in all cases and contained abundant collagen and well arranged fibroblasts. Focal areas of leukocytic infiltration were observed in these scars, but the inflammation present was chronic and localized. Healing was frequently complete by the time the animal was killed.

EFFECTS OF SODIUM CITRATE IN CONCENTRATED PLASMA

Sodium citrate binds ionic calcium rapidly, and for this reason it is commonly used as an anticoagulant. The excess sodium citrate in the plasma, above that bound to calcium, is capable of binding calcium in the blood stream. The binding effect on the calcium in the blood stream has been demonstrated [12] to be transient because the citrate is oxidized and the calcium liberated. Therefore, the organism after a sublethal intravenous injection of sodium citrate solution reverts rapidly to the preinjection state in so far as calcium ions are concerned. The citrate forms an alkaline ash which particularly tends to alkalinize excreta such as urine.

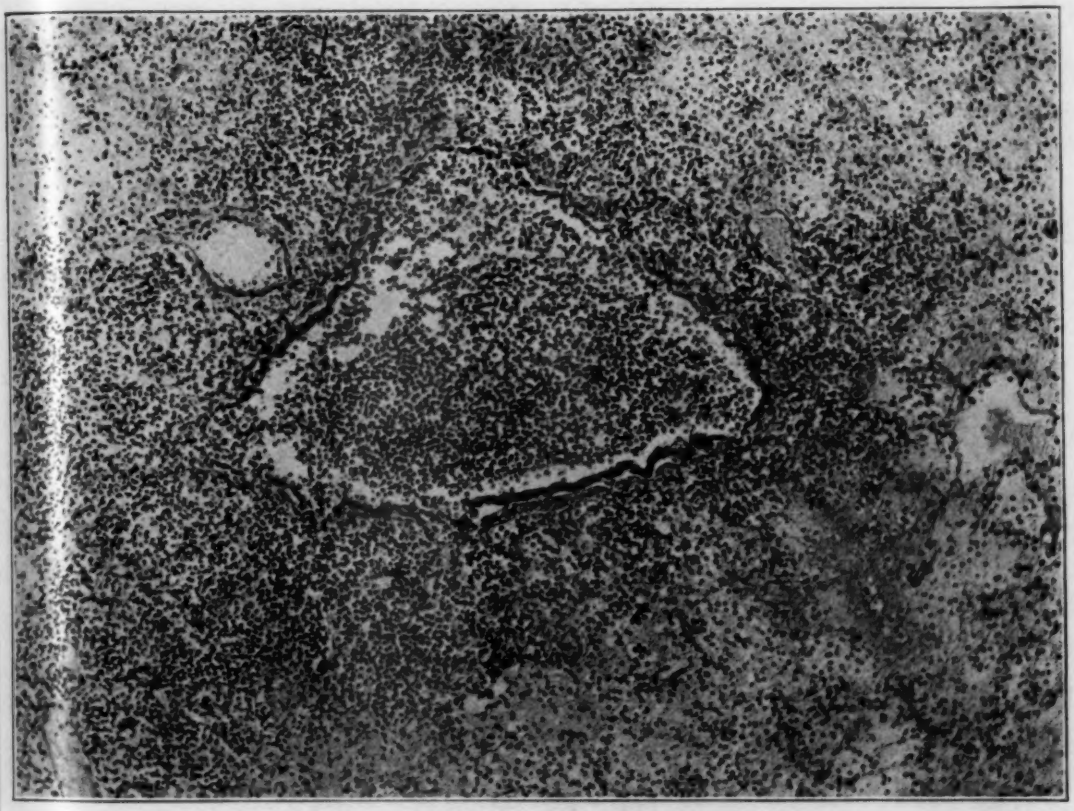

Fig. 4.—Dog 10, group 1 (amputation; no protein therapy); died ten days later; photomicrograph of the same lung as in figure 3, showing patch of bronchopneumonia superimposed on pulmonary edema.

The development of a calcium ion deficiency (manifested in the carpopedal spasm of tetany) after an intravenous dose of sodium citrate depends on the amount of citrate given per unit of time and on the calcium ion reserve of the recipient.[13] The present indications are that the calcium reserve is not sufficiently

12. Salant, W., and Wise, L. E.: The Action of Sodium Citrate and Its Decomposition in the Body, J. Biol. Chem. **28**:27-58 (Dec.) 1916.

13. The state of the calcium ion reserve during shock, to our knowledge, has not been as completely studied as that of other ions, such as the potassium ion. G. W. Duncan's paper (Inorganic Phosphorus Content of the Serum in Shock, Arch. Surg. **46**:214-223 [Feb.] 1943)

(Footnote continued on next page)

depleted to constitute a complete contraindication to the use of citrated plasma in shock. This conclusion has been reached through a series of studies on the use of concentrated citrated plasma during shock in human beings and experimental animals, including the present studies. The solution must be used judiciously, particularly for small animals, in order to avert tetany and other more serious complications (such as cardiac standstill). Thus the amount of sodium citrate given per unit of time becomes the important factor. With dogs the doses of concentrated plasma must be given periodically, in order to allow for clearance of the blood stream of citrate and for accommodation of the circulatory system to the action of the concentrated solution.

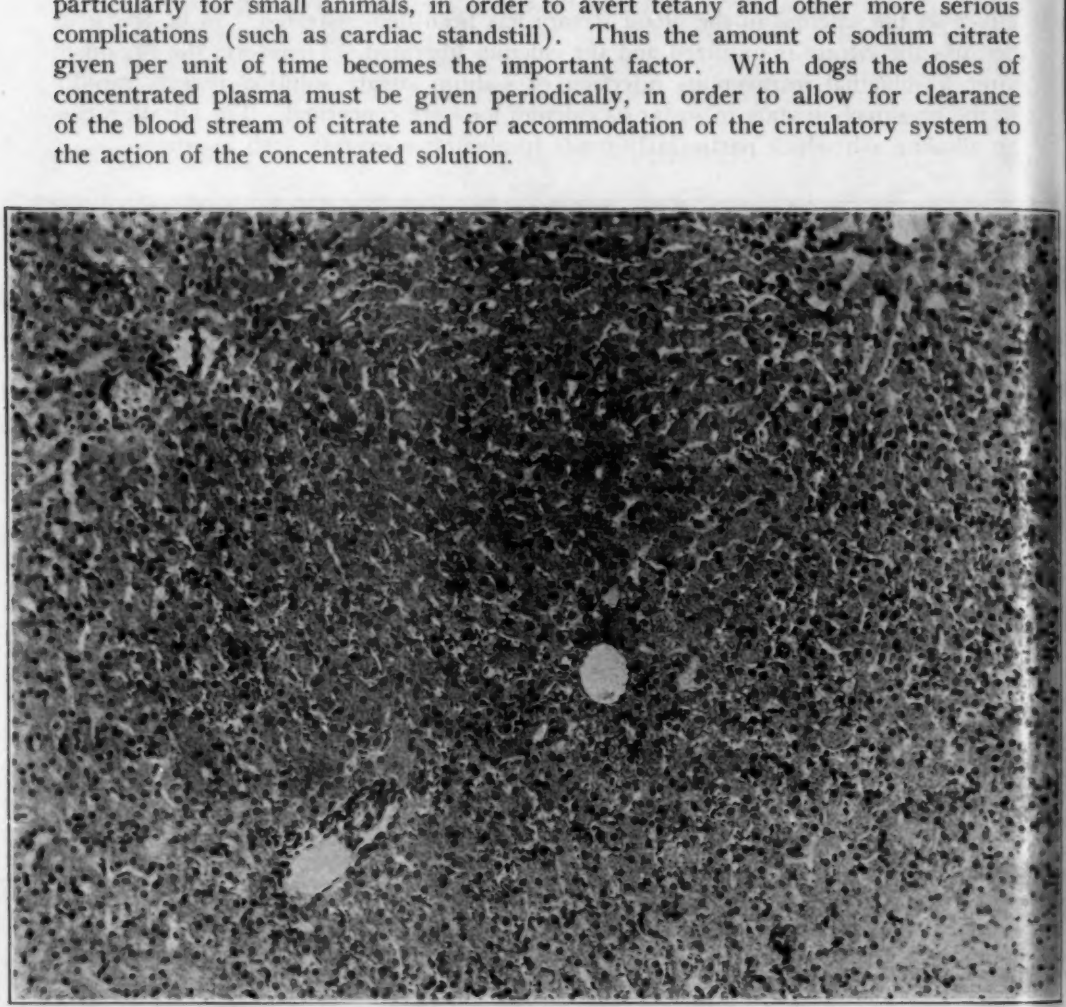

Fig. 5.—Dog 6, group 3 (amputation—protein therapy); lived; same dog as in figure 1; photomicrograph of the liver showing normal appearance, including darker and lighter zones. The width of the polygonal cells near the central vein is normal, and venosinusoidal hyperemia is absent.

In the present experiments 17 animals received concentrated citrated plasma. We were able to prevent or initiate tetany at will. Most of the 5 cc. doses (given in ten seconds) were spaced two to three minutes apart. Whenever 10 cc. doses

demonstrated conclusively an elevation of inorganic serum phosphate during shock and its development. The usual inverse relation to calcium at present appears unlikely, since the presence of a decrease in renal excretion should upset the usual reciprocal relation between these two substances. This view is supported by the observation of V. H. Moon (The Vascular and Cellular Dynamics of Shock, Am. J. M. Sc. **203**:1-18 [Jan.] 1942) that in shock the blood calcium is increased.

were repeated every thirty to sixty seconds a severe spasm of tetany resulted sooner or later. The intravenous injection of 10 cc. of concentrated plasma in ten seconds constitutes too rapid an injection for dogs this size, for reasons to be mentioned hereinafter.

In several animals muscular tremors or fibrillations developed, involving the tongue and scattered muscles elsewhere. The fibrillations were probably based on a transient calcium deficiency, since they disappeared shortly after the therapy was concluded. This reaction, apparently a milder degree of tetany, occurred with some of the 5 cc. doses and signified that even some of these were spaced too closely together.

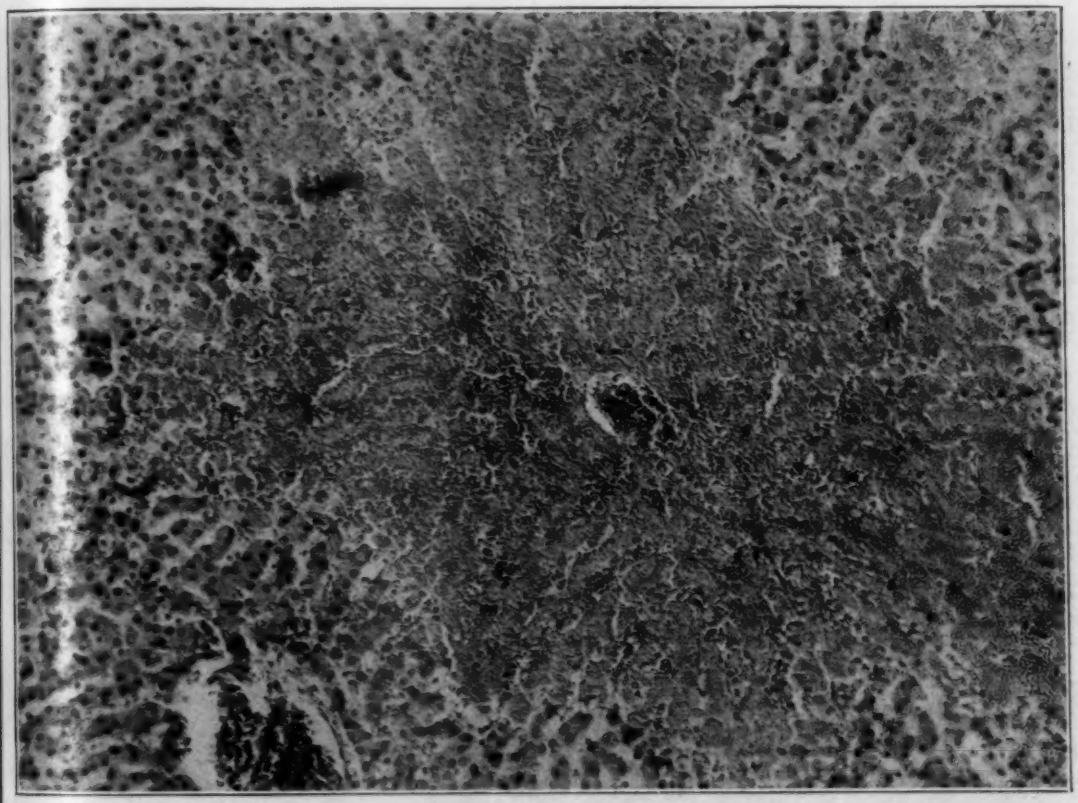

Fig. 6.—Dog 8, group 2 (protein therapy; no amputation); died in shock; photomicrograph of the liver showing coagulative necrosis of the central and midzonal portions of the lobule of the liver. One extension of this necrotic area became continuous with similar necrosis of an adjacent lobule. Over 50 per cent of the liver in this section of tissue was necrotic. The nuclear substance of the necrotic cells has disappeared.

Extreme caution must be exercised in interpreting the effects of citrate on dogs in terms of human beings. This care is necessary not just because one is dealing with two separate species. The dog is much lower in body weight; the vascular bed is smaller and the blood volume is much less. It is easy to inject 50 cc. of concentrated plasma into a dog weighing 10 Kg. in one minute, as we have done in the past.[14] To administer a dose proportionate to the body weight of a

14. Muirhead, E. E.; Ashworth, C. T., and Hill, J. M.: The Therapy of Shock in Experimental Animals with Plasma Protein Solutions: I. Concentrated Plasma as a Hemodiluting Agent, Surgery **12**:14-23 (July) 1942.

normal man weighing, let us say, 80 Kg., one would have to inject 400 cc. of concentrated plasma in one minute. We consider this rate very difficult to attain with ordinary syringes and needles, and although we have no experience with such rapid administration to human subjects, bad effects would be expected.

We have advocated the intravenous injection of 50 to 100 cc. of concentrated plasma to patients in shock in one to five minutes, with an interval of ten to twenty minutes between injections.[15] In actual practice usually 100 cc. is given in five minutes.[15c] If this rate is suitable for a human being weighing 80 Kg., a dog weighing 10 Kg. would require 2.5 cc. of concentrated plasma per minute for the period of actual administration, with intervening periods for circulatory accom-

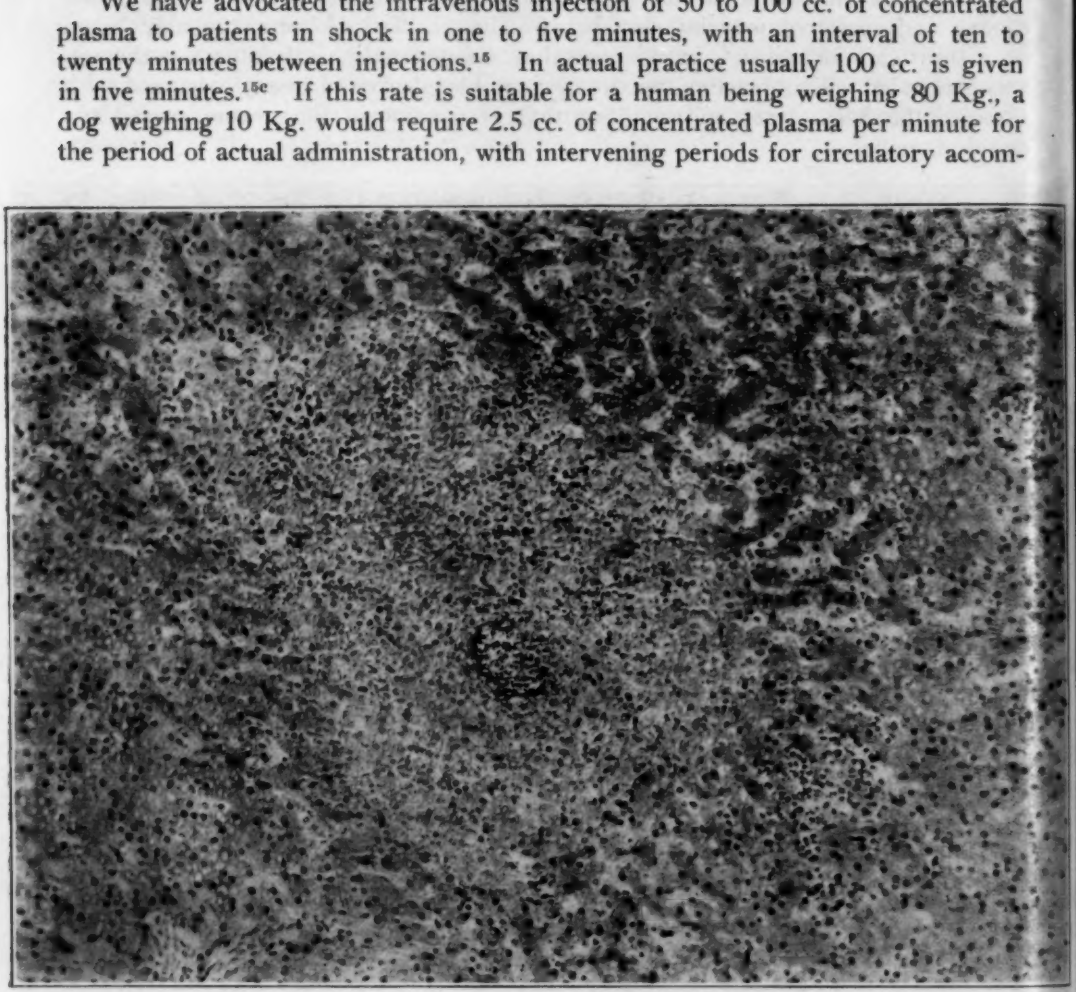

Fig. 7.—Dog 3, group 1 (amputation; no protein therapy); died in shock; photomicrograph of the liver showing central necrosis and moderate fatty degeneration of viable liver cells. There is slight infiltration of the necrotic area by polymorphonuclear neutrophilic leukocytes. Once more there is a notable absence of nuclear remnants in the necrotic liver cells.

modation. The average rate of injection in the present experiments was 5 to 10 cc. in ten to thirty seconds. This rate, which was far beyond the human rate, admittedly exceeded the limits we had set and will be discussed under the depressor effect.

---

15. (*a*) Hill, J. M.; Muirhead, E. E.; Ashworth, C. T., and Tigertt, W. D.: The Use of Desiccated Plasma with Particular Reference to Shock, J. A. M. A. **116**:395-402 (Feb. 1) 1941. (*b*) Hill, J. M., and Muirhead, E. E.: The Use of Desiccated Plasma in Urology, J. Urol. **47**:387-394 (March) 1942. (c) Muirhead, E. E.; Ashworth, C. T., and Hill, J. M.: The Use of Human Plasma Protein Solutions in Surgery, South. Surgeon **11**:413-431 (June) 1942.

In conclusion, tetany resulted in the present experiments only when the injections were spaced too closely together. It appears, then, from practical experience that the judicious use of concentrated plasma for shock in small animals or in human beings need not be accompanied by tetany or other acute effects of sodium citrate on the circulation.

TRANSIENT DEPRESSOR EFFECT

Concentrated serum containing 15 Gm. per hundred cubic centimeters of protein has been observed by us [8] to produce a transient depression of the mean arterial pressure in dogs when doses of 5 to 20 cc. are given intravenously in five

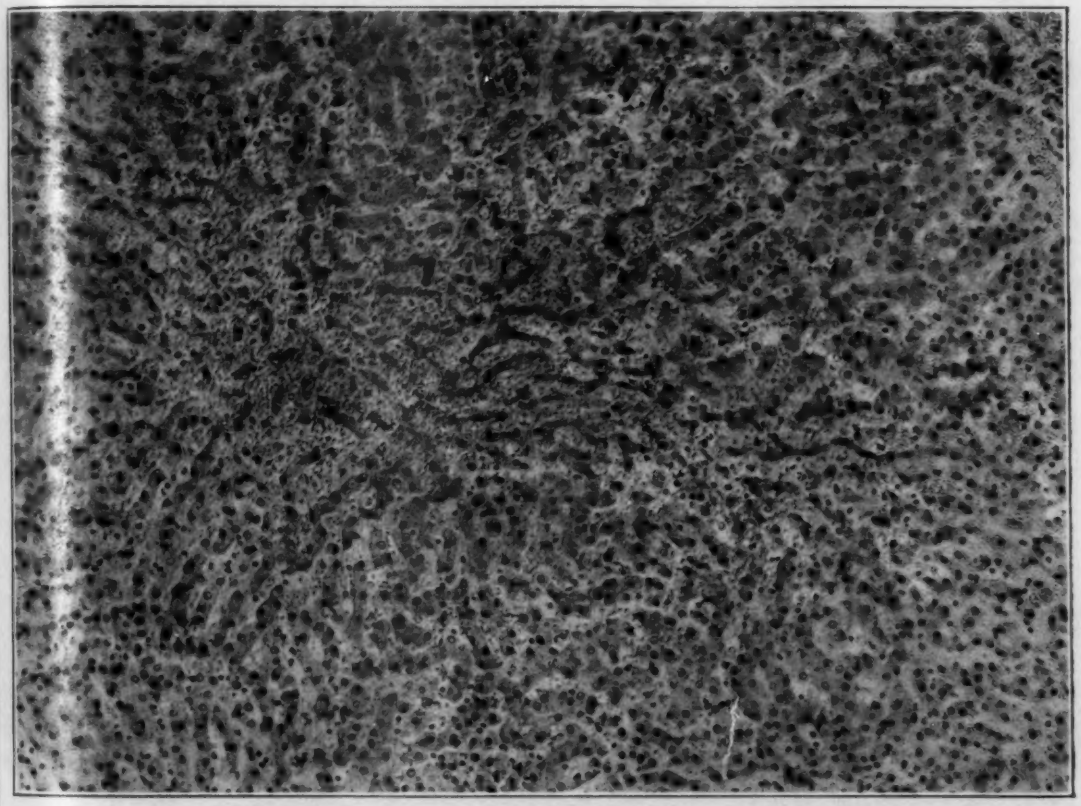

Fig. 8.—Dog 4, group 2 (protein therapy; no amputation); died in shock; photomicrograph of the liver showing atrophy of the cord cells in the central portion of the lobule. The sinusoids appear considerably widened. Compare these cells with those in figure 5.

to thirty seconds. This effect varied somewhat from animal to animal but could be elicited consistently when larger doses (15 to 20 cc.) were given rapidly (ten seconds). These observations were substantiated in the present experiments with both concentrated plasma and serum given to animals with normal, slightly elevated or slightly depressed arterial pressures.

The depressor effect consisted of a transient drop in mean arterial pressure followed by complete recovery. With subjects whose arterial pressure was depressed, recovery was associated with a rise in pressure above the initial level. The entire effect lasted thirty to sixty seconds. When larger doses were given, the pressure was lowered by 15 to 25 mm. of mercury. Occasionally in instances

when the original pressure was high (190 to 200 mm. of mercury) the decrease amounted to as much as 40 mm. of mercury. Hyperpnea at times accompanied the effect.

In this connection a technical point related to the sodium citrate solution used in the mercury manometer setup should be remembered. When the arterial pressure drops, citrate solution is forced into the carotid artery and when the drop is considerable, enough sodium citrate may dam back into the heart to precipitate a citrate effect and exaggerate the effect due to sodium citrate in the plasma. To avoid this complication we have used a heparin solution in other experiments.

This depressor effect has been studied further, and the results form the basis for a separate report.[16] For the present we should like to point out that a similar

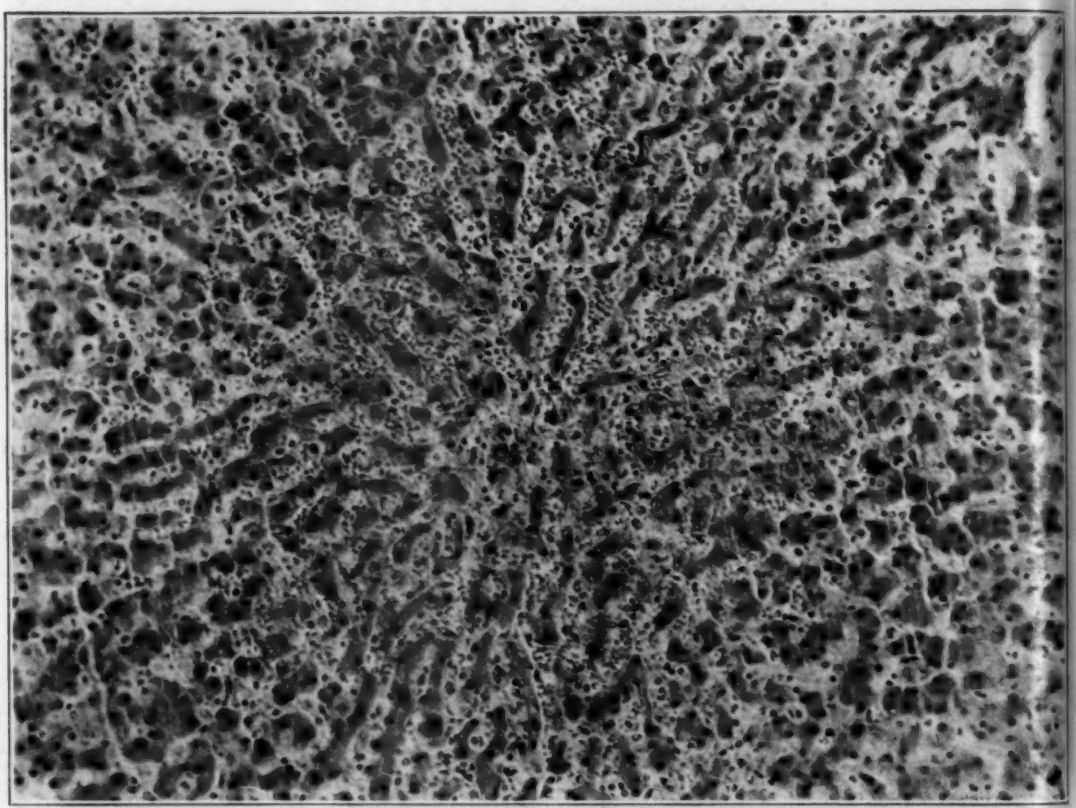

Fig. 9.—Dog 7, group 1 (amputation; no protein therapy); died in shock; photomicrograph of the liver showing central atrophy of the hepatic cells. As the hepatic cords approach the region of the central vein they become thin and narrow, so that frequently the nuclei are adjacent to the limiting cell membrane. There are focal areas of fatty degeneration.

depressor effect can be elicited in normal dogs or dogs suffering from freezing shock or hypotension due to hemorrhage by the rapid injection of any of the following solutions: concentrated plasma and serum, 50 per cent solution of dextrose, 10 per cent solution of sodium chloride, 3 per cent solution of sodium chloride and 20 per cent solution of acacia. In our experience, isotonic solutions

16. Muirhead, E. E.; Lacke, R.; Bunde, C. A., and Hill, J. M.: The Depressor Effect Following the Very Rapid Intravenous Injection of Concentrated (Hypertonic) Solutions to Dogs, unpublished data.

in the same volume and rate have not precipitated a similar effect. Isotonic solutions given in larger, comparable volumes elicit a different depressor response.

The concentrated solution must reach the cardiac-pulmonary region rapidly in order to effect a response. The injection of 10 to 15 cc. in forty-five to ninety seconds instead of five to fifteen seconds has consistently failed to produce this response.

It appears, therefore, that the speed of injection and the concentration of the solutes are the main factors producing this response. In the present experiments most of the injections were given sufficiently rapidly to initiate the transient depression, but any single injection that was given at a relatively slower rate

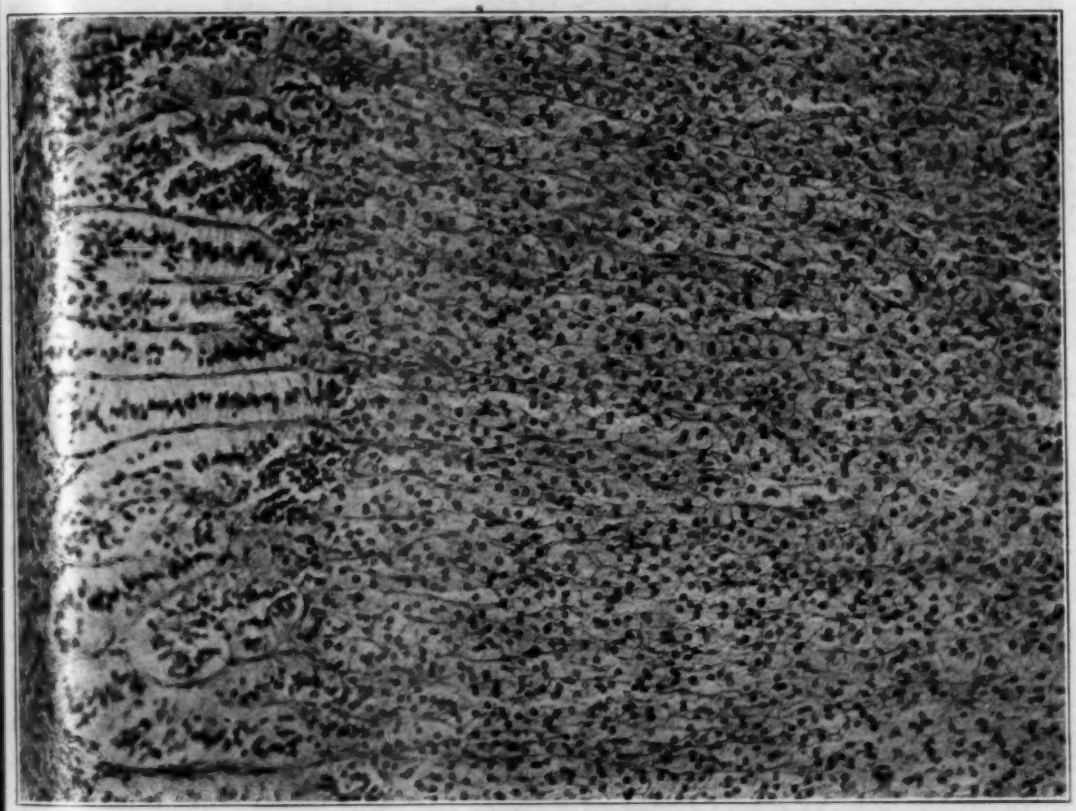

Fig. 10.—Dog 6, group 3 (amputation; protein therapy); lived; photomicrograph of an adrenal gland showing capsule, zona glomerulosa and zona fasciculata. The appearance is normal, with cells well filled with lipid, which gives them a foamy appearance.

failed to produce it. According to our criteria, however, the end results of the injections in each instance appeared to be beneficial to the circulation.

In this connection, as was the case with the citrate reactions, it would seem that caution is needed in interpreting the results in terms of human beings. If the previous basis for comparison is used, it appears that doses as high as 300 to 600 cc. of concentrated plasma given in one minute to human adults weighing 80 Kg. would be required to effect similar changes. Therefore, the margin of safety in man appears great, but care seems necessary in studying the treatment of experimental shock in animals with concentrated plasma and serum, since it is

easy to overtax the animals' ability to handle the solutions. Intermittent injections of 2.5 to 15 cc. given in forty-five to one hundred and twenty seconds seem to be adequate.

GENERAL COMMENT

Severe freezing of one hind extremity of a dog produces widespread damage to capillaries and tissues after thawing. In the 2 dogs which survived for a few days the extent of the injury was emphasized by the fact that the limb became completely gangrenous. This injury leads to a series of events culminating in severe oligemia and cellular damage to the viscera. Previous study [8] indicated that

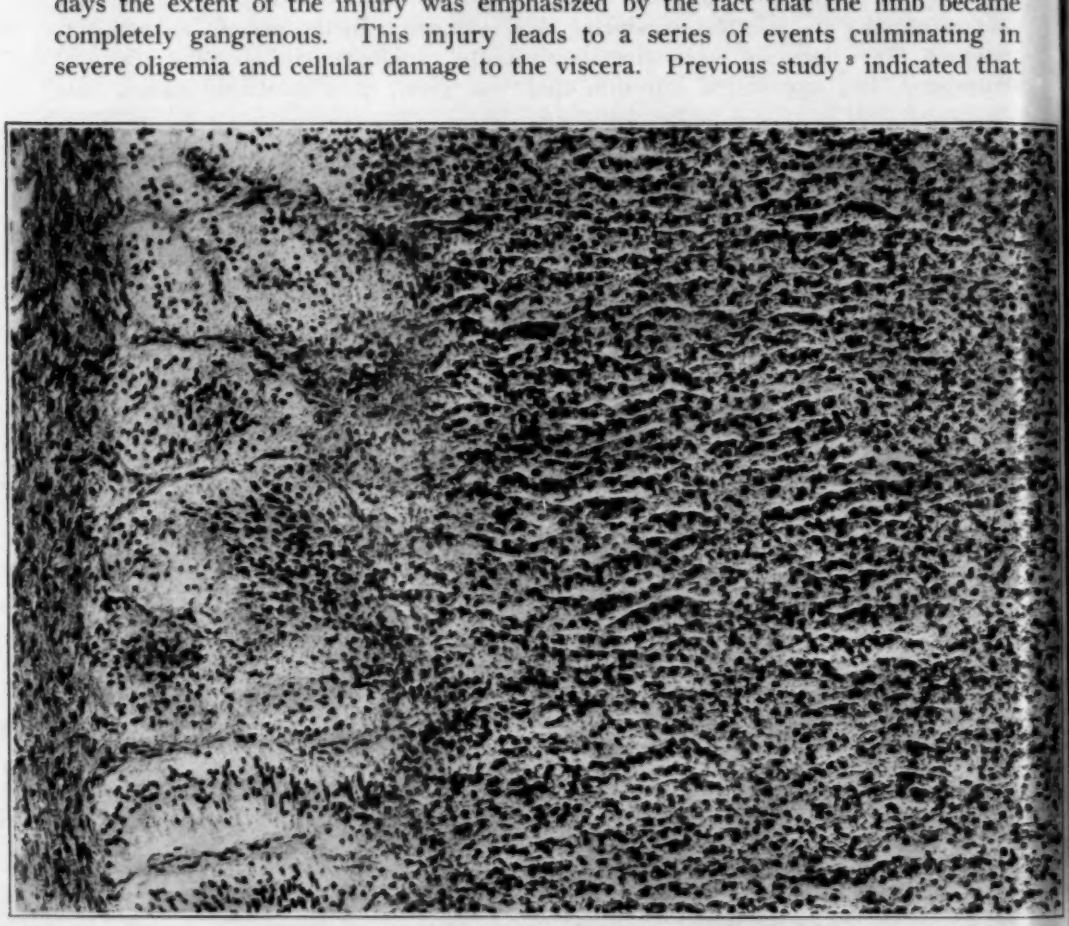

Fig. 11.—Dog 1, group 2 (protein therapy; no amputation); died in shock; photomicrograph of an adrenal gland showing the capsule, zona glomerulosa and zona fasciculata. There is a considerable difference from figure 10. The cells of the zona fasciculata are narrow and dense and display a marked decrease in lipid content. There are scattered polymorphonuclear neutrophilic leukocytes.

visceral damage became evident beyond the fourth hour. The present experiments indicate that removal of the limb between the third and the fourth hour is not in itself sufficient to assure recovery (group 1). Only 2 animals in this group marshaled recovery mechanisms adequate to cope with damages wrought by the shocking procedure plus operation. In the majority (8 of 10) the pathogenesis of shock continued unhampered, or at the most they lingered a few days only to die of complications related to the shocking procedure. The results obtained with group 2 seem to indicate that a single replacement of the plasma volume and

circulating proteins during the apparent borderline period of advanced visceral damage likewise fails to bring about life-saving recovery if further therapeutic measures are not taken. A combination of removal of the damaged site plus immediate plasma volume and protein replacement (group 3) was successful in preventing the further advancement of the pathogenesis of shock and allowed for complete recovery. In group 3, moreover, the demonstrated lack of active or residual cellular damage and the absence of evidence of previous cellular damage with repair of the viscera indicated that the prevention of fatal shock occurred before pathologic changes were sufficiently pronounced or advanced to overwhelm the organism.

Fig. 12.—Dog 3, group 1 (amputation; no protein therapy); died in shock; photomicrograph of an adrenal gland showing the capsule, zona glomerulosa and zona fasciculata. There is a decrease in the lipid content, which is not as marked as in figure 11, and scattered leukocytes are seen.

The present experiments seem to afford no new evidence to settle the controversy between those who hold that shock is due to toxemia [17] and those who maintain that it is due to local loss of fluid from the plasma.[18] The visceral lesions in the dogs of group 1 and group 2 were similar; that is, no deviation in the type of lesion resulted from the removal of the damaged limb before the apparent

17. Moon, V. H.: Shock: Its Dynamics, Occurrence and Management, Philadelphia, Lea & Febiger, 1942.

18. Blalock, A.: Principles of Surgical Care: Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940.

borderline period of advanced visceral damage. It seems true that the lesions were similar to the type encountered whenever there is stagnation of the circulation, as those who have examined autopsy material from patients who had passed through a period of failure of the right side of the heart would verify, or a decrease in transport of oxygen to the tissues. Thus the hepatic lesions resembled the lesions of passive hyperemia described by Lambert and Allison,[10] the lesions of severe anemia described by Rich [19] and certain lesions due to experimentally induced anoxia.[20] On the other hand, certain toxic agents conveyed by the blood stream are known to produce central necrosis of the liver.[21] Moon [11] has emphasized the similarity in the appearance of the visceral lesions due to generalized passive

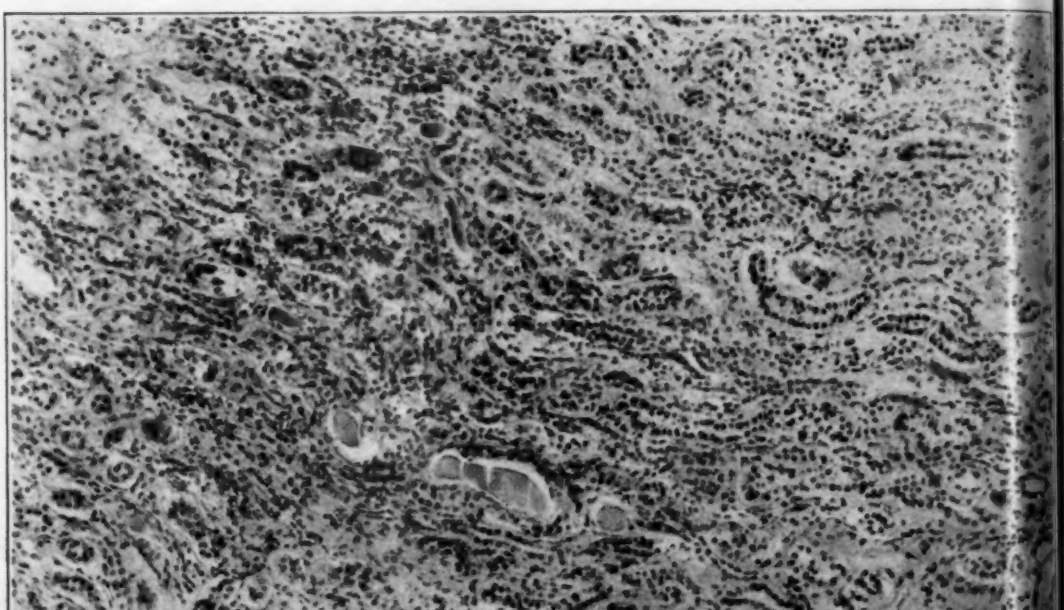

Fig. 13.—Dog 3, group 1 (amputation; no protein therapy); died in shock; photomicrograph of a kidney showing hyaline casts in the medullary tubules. Granular protein material was observed in the capsular spaces of Bowman's capsule.

hyperemia, asphyxia and shock. The only evidence that a sustained hypoxemia resulting from the oligemia was solely responsible for the visceral lesions encountered in the present experiments is the similarity between these lesions and those resulting from an induced simple anoxia. One cannot question the concept

19. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338-377 (Dec.) 1930.

20. McIver, M. A., and Winter, E. A.: Deleterious Effects of Anoxia on the Liver of the Hyperthyroid Animal, Arch. Surg. **46**:171-185 (Feb.) 1943.

21. MacCallum, W. G.: A Text-Book of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1936, p. 298.

that absorbed toxic agents are responsible for the parenchymatous damage and pulmonary edema (the toxic theory) on such meager collateral evidence. Nevertheless, one could not but be impressed with the amount of fluid in the damaged limb during these experiments, whether treatment was given or not. The limbs of the dogs in group 2 were huge. Seven specimens of the abundant subcutaneous fluid at the site of damage when analyzed yielded an average protein concentration of 4.7 Gm. per hundred cubic centimeters. This fluid was free from red cells and approached the circulating plasma in protein content. Therefore, the escape of protein-containing fluid into the damaged limb appeared to play a prominent role in the pathogenesis of fatal shock of dogs in groups 1 and 2.

Fig. 14.—Dog 2, group 3 (amputation; protein therapy); lived; photomicrograph of skin and subcutaneous tissue of the frozen-thawed site (amputated limb) showing edema of the subcutaneous tissues. The connective tissue fibers are separated by a granular, pink precipitate similar to that observed in the alveoli of the lungs in pulmonary edema. This precipitate represents a protein-containing fluid.

The work of Sir Thomas Lewis [22] has demonstrated the presence of substances at the site subjected to freezing and thawing capable of dilating the capillaries and increasing their permeability to plasma colloids and has made it clear that this is a mechanism likely to be involved in the process of local fluid loss. Previous studies [1] indicated that the loss of fluid at the site of freezing and thawing appeared to be predominant before generalized capillary atony and pulmonary edema

22. Lewis, T., and Love, W. S.: Vascular Reactions of Skin to Injury: III. Some Effects of Freezing, of Cooling and of Warming, Heart **13**:27-60 (Aug.) 1926.

appeared. Of course, it was not established whether the absorption of the harmful agents from the damaged site was responsible for the ultimate generalized visceral damage or whether hypoxemia was solely causative. In this connection, therefore, one agrees with the compromise offered by Solandt and Best [23] and based on their study of other types of shock-producing injuries. They stated that in shock due to freezing local loss of fluid is a major etiologic factor, but that "almost certainly other unknown factors are operative." [23]

The controversies regarding the pathogenesis of shock are once more alluded to in order to emphasize the difficulties involved in explaining the results of the present experiments.

Fig. 15.—Dog 2, group 3 (amputation; protein therapy); lived; photomicrograph of the healing amputation site ten days after the operation. There are many fibroblasts in parallel arrangement, with abundant intercellular material. The skeletal muscle is normal in appearance. Same dog as in figure 14.

The proponents of the toxic theory would explain the results by claiming that in group 3 when the toxin-bearing area had been removed the improvement of the circulation by intravenous protein therapy allowed for recovery from the early damage due to the absorbed toxins, that in group 2 the toxin-bearing area continued to contribute harmful agents leading to fatal shock (also an explanation

23. Solandt, D. Y., and Best, C. H.: Studies on the Etiology of Traumatic Shock, in Mudd, S., and Thalhimer, W.: Blood Substitutes and Blood Transfusion, Springfield, Ill., Charles C Thomas, Publisher, 1942.

for the greater severity of hepatic lesions) and that in group 1, without an improved circulation, the organism was unable to cope with the early damage by toxins and the superimposed hypoxemia. Those who uphold the theory of local loss of fluid would claim that in group 3 the removal of the damaged extremity did away with the site of plasma loss and that with therapy the circulation was reestablished and maintained before the onset of irreversible failure, so that recovery ensued; that in group 2 the site of local fluid loss was maintained and oligemia and fatal shock were produced, and that in group 1 the lowered circulating volume following amputation was sufficient to allow hypoxemia to produce the generalized changes.

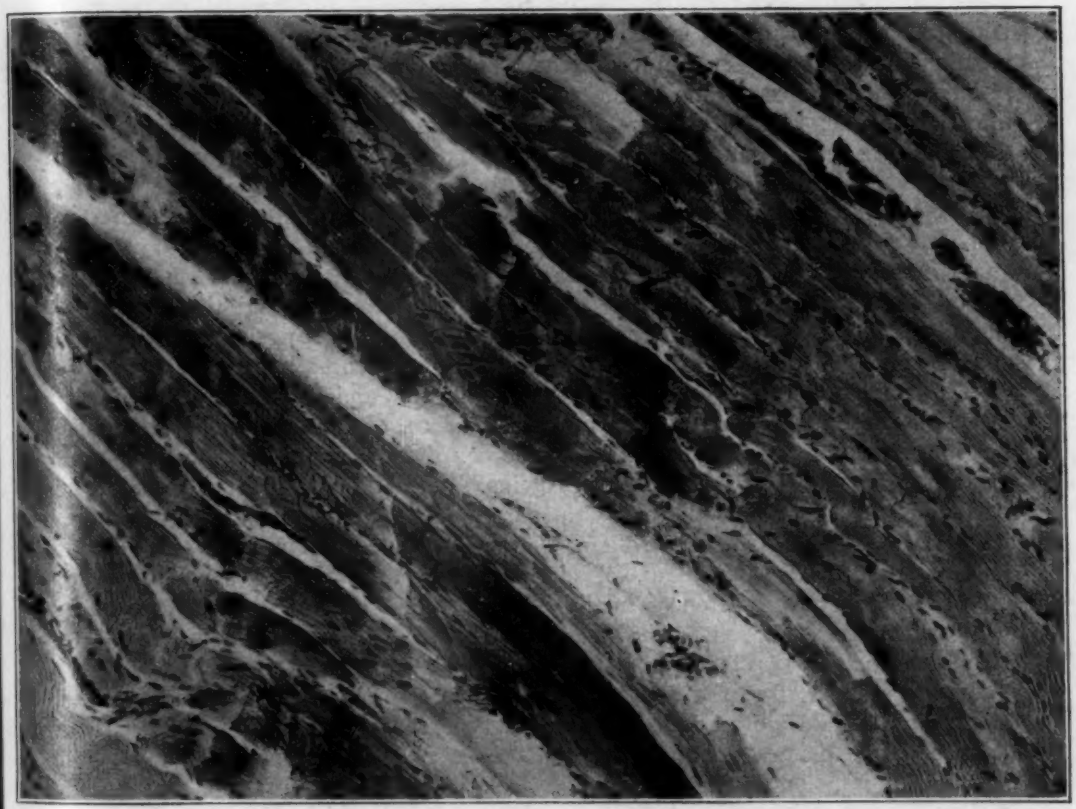

Fig. 16.—Dog 2, group 2 (protein therapy; no amputation); died in shock; photomicrograph of somatic musculature remote from the frozen-thawed site. There are several venules stuffed with red blood cells and an occasional open capillary. There is no edema; the muscle fibers are normal in appearance, and most of the capillaries are closed.

With regard to other controversial features in the field of shock therapy, we feel more certain of several deductions. There should be no doubt that concentrated plasma and serum, properly prepared and administered, are capable of improving the circulation during shock by increasing the plasma volume and circulating proteins. By all present indications, the action occurs at capillary sites where fluid is withdrawn into the circulation. A previous study [8] indicated that the venous hemoglobin is not an accurate guide to the degree of increase in plasma volume, since greater numbers of red cells seemed to be released into the general

circulation from capillary sites. Such an event would explain the fact that in the present experiments the venous hemoglobin concentration failed to return to the control level, even in group 3, despite a minor degree of loss of blood during the operation. The absent or slight elevation of the recipient's plasma protein concentration in the presence of intravenous injections of a concentrated protein solution is indicative of the passage of fluid into the plasma stream.

The observations presented in this paper and in others [24] are in disagreement with the observations of Mahoney, Kingsley and Howland.[25] These investigators observed essentially no beneficial effects on the circulation after the intravenous administration of concentrated plasma to dogs in a state of shock resulting from intestinal trauma and reasoned that in the presence of the circulatory failure of shock concentrated plasma is unable to draw fluids back into the circulation. The solutions were not injected intermittently but given continuously by vein. The plasma protein concentration of the recipient was elevated, and it was stated that in certain of the animals receiving 200 cc. of concentrated plasma as a prophylactic dose (begun at the same time as trauma), "the plasma volume would remain essentially unchanged during the injection, but in spite of this the blood pressure fell, followed by death of the animal." It was not stated whether the plasma was prepared with sodium citrate, and the protein concentration of the material given and the specific weights of the animals given the solutions were not reported. It would seem that variations between the amounts of protein and the technics of administration used by us and those used by Mahoney, Kingsley and Howland and us have had a great deal of influence on the differences in results.

The therapeutic doses used by Mahoney, Kingsley and Howland were 45 to 50 cc. of concentrated plasma and as much as 700 cc. of dilute plasma for animals weighing "from 15 to 25 Kg." Usually 30 cc. of four times concentrated plasma contains between 10 and 12 Gm. of proteins. The 700 cc. of dilute serum, with a protein concentration of 3 to 4 Gm. per hundred cubic centimeters, contained between 21 and 28 Gm. of protein. Inasmuch as certain animals exhibited a deficit of as much as 37 Gm. of circulating proteins during shock, one can appreciate the gross differences in the replacement of lost circulating proteins by these two volumes of solutions and consequently the grossly different effects on the circulation.

If one assumes that the plasma solutions were prepared with sodium citrate, one can appreciate why a fatal termination occurred for certain animals without changes in the plasma volume. Ivy and his associates [26] observed that a single replacement infusion of citrated plasma after a copious hemorrhage was not as efficient as one of heparinized plasma and reasoned that the effects of the citrate were responsible for the difference. Since a greater amount of calcium is bound per unit of time by the injection of concentrated or of normal plasma than by the injection of dilute plasma, the severity of the effects would necessarily be greater with the former two solutions. On previous occasions [14] we observed death of animals who had been subjected to exceedingly rapid administration of concentrated citrated plasma.

---

24. Muirhead, Ashworth, Kregel and Hill.[8] Muirhead, Ashworth and Hill, footnotes 14 and 15*c*.

25. Mahoney, E. B.; Kingsley, H. D., and Howland, J. W.: The Treatment of Experimental Shock by the Intravenous Injection of Dilute, Normal and Concentrated Plasma, Surg., Gynec. & Obst. **74**:319-325 (Feb., no. 2 A) 1942.

26. Ivy, A. C.; Greengard, H.; Stein, I. F., Jr.; Grodins, F. S., and Dutton, D. F.: The Effect of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage, Surg., Gynec. & Obst. **76**:85-90 (Jan.) 1943.

The recent observations of Levinson, Weston, Janota and Necheles [27] that the arterial pressure is depressed temporarily after injections of concentrated serum are apparently of the same nature as those discussed under the heading of transient depressor effect, since Levinson, Weston, Janota and Necheles injected 50 cc. of the concentrate in one minute into dogs in hemorrhagic shock. In an earlier report [14] we observed harmful effects from a similar rate of injection of concentrated plasma but attributed most of the results to the sodium citrate in the solutions. It appears evident now that at least part of the ill effects resulted from the too rapid administration of the concentrated solutions.

SUMMARY AND CONCLUSIONS

Severe freezing of one hindlimb, an injury previously determined to produce fatal shock in dogs within an average of eight hours, was produced, and the following three therapeutic procedures were instituted for groups of 10 dogs each: In group 1, the damaged extremity was amputated between three and two-tenths hours and three and nine-tenths hours (average) after the freeze was terminated and the effects observed; in group 2, intravenous injections of concentrated plasma, in amounts previously determined to effect a sufficient replacement of the plasma volume was instituted between four and two-tenths and four and nine-tenths hours and the effects observed; in group 3, the damaged limb was amputated between three and three-tenths and three and ninety-nine hundredths hours (average) after the freeze was terminated and adequate intravenous injections of concentrated plasma were instituted between four and three-tenths and four and eight-tenths hours (average). Previous study had revealed that advanced visceral damage appeared after the fourth hour.

The following results were obtained: in group 1, 8 of 10 dogs died after a few hours in shock or after a few days of complications resembling the shock picture; in group 2, all 10 dogs died in shock, 8 of them within a relatively few hours; in group 3, all dogs lived and appeared healthy subsequently.

Concentrated plasma increased the circulating plasma volume and circulating plasma proteins by withdrawing fluids into the plasma stream. This effect was demonstrated by a meager or no elevation of the recipient's plasma protein concentration.

As has been previously observed, the degree of venous hemodilution following the administration of concentrated plasma was not complete, although one would expect it to be so after an adequate replacement of plasma volume. This phenomenon seemed to indicate the presence of greater numbers of red blood cells, possibly released from capillary sites, in the general circulation.

Histopathologic studies revealed that the visceral lesions of groups 1 and 2 were similar. The hepatic necrosis was unique in that we had not observed such severe damage in this type of shock before, possibly because the animals lived longer than those used for previous studies. The damage to the viscera of the dogs in groups 1 and 2 demonstrated what was prevented in group 3. The viscera of the dogs in the latter group were normal and revealed no residual damage or evidence of damage with repair. Apparently the prevention of visceral damage was complete.

Emphasis has been placed on the effects of sodium citrate in binding the calcium in the plasma, because differences of opinion appear to have resulted from this

27. Levinson, S. O.; Weston, R. E.; Janota, M., and Necheles, H.: Effects of Concentrated Serum in Contrast to Iso-Osmotic Plasma on Normal and Dehydrated Dogs in Shock, Surgery **12**:878 (Dec.) 1942.

property. It has been stressed that concentrated plasma should be injected by vein in intermittent doses for two reasons: (1) to allow for oxidation of the citrate and (2) to allow for accommodation of the organism to the concentrated solutions.

The transient depressor effect of concentrated solutions when they are injected very rapidly by vein into small animals (dogs) has been discussed. The difference in response of small animals and adult human beings has been pointed out.

The results have been discussed with reference to two leading theories of the pathogenesis of shock, that of toxemia and that of local loss of plasma. The absorption of harmful agents from the damaged site could not be questioned on the basis of the results obtained, but local loss of fluid appeared to be a prominent etiologic factor.

Mr. Kenneth Stemmle, a fourth year student in the medical school, assisted in these experiments as his senior year problem. The photomicrographs were prepared by Mr. Lewis Waters of the Medical Arts Department. Miss Mary Seamen prepared the tissue sections. Miss Inagene Blair determined the protein concentrations.

3301 Junius Street.

FROZEN SHOULDER; PERIARTHRITIS; BICIPITAL TENOSYNOVITIS

ROBERT K. LIPPMANN, M.D.
Orthopedist to Mount Sinai Hospital
NEW YORK

Of the various conditions known to affect the periphery of the shoulder joint, least is known about periarthritis, or frozen shoulder. Although the illness was clinically identified many years ago, it continues to be known by an inaccurate name, its pathology remains mysterious and views regarding its therapy are divergent and confusing. The present study is concerned with evidence in support of the contention that the basic lesion in so-called periarthritis or frozen shoulder is bicipital tenosynovitis. Correlation of the clinical and pathologic observations to be herewith reported clarifies the mechanism which underlies the illness, explains its remarkable spontaneous cure and furnishes a sound basis on which conservative and surgical therapy may be planned.

CHRONOLOGY

The contributions of Duplay [1] at the close of the nineteenth century represent the first effort to distinguish "humeroscapular periarthritis" from the vague general classification "arthritis." The disease that Duplay described corresponds clinically to what now is termed "frozen shoulder," and he attributed it to subacromial bursitis. By the name "periarthritis" Duplay meant something more than a lesion peripheral to the shoulder joint proper. He regarded the subacromial bursa as an accessory shoulder joint, or periarthros, and to Duplay periarthritis meant specifically an inflammation of this structure. Duplay recommended manipulation with the patient under anesthesia for alleviation of the stiffness. These papers were published prior to and coincident with the invention of the roentgen ray apparatus, so that the author was unable to recognize and distinguish those shoulders with calcific deposits. In the decade following, the use of roentgen examinations became widespread. Calcified deposits in painful as well as in asymptomatic shoulders were encountered, and in 1907 Baer [2] and Painter [3] published the first papers in this country advocating removal of the deposits for relief of pain. The greater part of the medical profession, however, was slow to accept the existence of any clinical distinction between painful shoulders with calcific deposits and those without them. The term "periarthritis" continued to be employed to describe many varieties of abnormal conditions of the shoulder, and subsequent literature is rich in controversial papers on the subject. Pleas for a pathologic interpretation of pain in the shoulder were frequently expressed (King and Holmes [4]), but as late as 1931

1. Duplay, S.: De la périarthrite scapulo-humérale, Rev. prat. d. trav. de méd. **53**:226, 1896; translated, M. Week **4**:253, 1896; On Scapulo-Humeral Periarthritis, M. Press **59**:571-573, 1900. Duplay wrote a monograph on scapulohumeral periarthritis in 1872, but I have been unable to locate this early paper.

2. Baer, W. S.: Operative Treatment of Subdeltoid Bursitis, Bull. Johns Hopkins Hosp. **18**:282-284, 1907.

3. Painter, C. F.: Subdeltoid Bursitis, Boston M. & S. J. **156**:345-349, 1907.

4. King, J. M., Jr., and Holmes, G. W.: Diagnosis and Treatment of Four Hundred and Fifty Painful Shoulders, J. A. M. A. **89**:1956-1961 (Dec. 3) 1927.

Mumford and Martin [5] and in 1932 Dickson and Crosby [6] published comprehensive papers on the subject and stated that they could observe no *clinical* difference between the two groups of cases. Although Mumford and Martin wrote, "In none of the very severe 'painful' shoulders in which there is a marked loss of function due to firm adhesions . . . did a deposit occur," this correct observation was incorrectly taken by the authors to indicate that the calcium deposits noted on roentgen examination are of no importance. Sporadic publications still appear [7] which indicate no appreciation of the clinical difference between the two groups of cases.

The comprehensive studies of Codman [8] served a threefold purpose in clarifying the situation. In the first place, Codman settled beyond further doubt that cases of pain in the shoulder associated with calcific deposits constitute a separate entity. Following his lead, those of us who have observed the rapid disappearance of symptoms after surgical removal of the deposits can no longer doubt their causal relationship to the pain. Secondly, Codman identified the ruptures of the supraspinatus tendon and so removed another large group of cases from the heterogeneous classification of periarthritis. In the third place, Codman described the clinical picture of frozen shoulder with such clarity that its clinical identification and separation from the other groups presented no further confusion. He appears to have been the first to call attention to the benign ultimate prognosis that characterizes the illness. Though Codman's [8] clinical description of the condition was most complete, the pathologic basis of the ailment was obscure to him, and he frankly admitted as much. Of his large book on the shoulder, only eight pages are devoted to the frozen shoulder, and he wrote: "These are common cases, but it does not take a long chapter for me to tell all I know about them." Codman believed that the cause of these painful shoulders lay in a "tendinitis of the short rotators," though he confessed this to be essentially a "hunch," and operation on several patients had revealed only "congestion in the floor of the bursa and occasional adhesions."

It was by exclusion, therefore, that periarthritis finally assumed the proportions of an entity. The identification of the disease due to calcific deposits in the shoulder left a large residue of cases of pain in the shoulder in which calcium deposits were not encountered. When the cases of rupture of the supraspinatus tendon were withdrawn from this residue, the greater number of those remaining could be classified as conforming to the clinical syndrome of periarthritis.

Coincident with Codman's clinical studies in Boston, interesting observations were being made by A. W. Meyer of Stanford University.[9] In the course of routine anatomic dissections of the shoulder, Meyer noted what he termed "attrition" lesions involving the long head of the biceps and the tissues in its vicinity. Thinning, fraying and fibrillation of the tendon were encountered with frequency (7 of

5. Mumford, E. B., and Martin, F. J.: Calcified Deposits in Subdeltoid Bursitis, J. A. M. A. **97**:690-694 (Sept. 5) 1931.

6. Dickson, J. A., and Crosby, E. H.: Periarthritis of the Shoulder: Analysis of Two Hundred Cases, J. A. M. A. **99**:2252-2257 (Dec. 31) 1932.

7. Michetti, G.: Contributo allo studio della periartrite spontanea della spalla, Minerva med. **2**:198-203, 1940.

8. Codman, E. A.: The Shoulder, Boston, The Author, 1934.

9. Meyer, A. W.: (*a*) Unrecognized Occupational Destruction of the Tendon of the Long Head of the Biceps Brachii, Arch. Surg. **2**:130-144 (Jan.) 1921; (*b*) Spontaneous Dislocation of Long Head of Biceps Brachii, ibid. **13**:109-119 (July) 1926; (*c*) Spontaneous Dislocation and Destruction of the Tendon of Long Head of Biceps Brachii, ibid. **17**:493-506 (Sept.) 1928.

60 cases).[9a] Dislocation of the tendon out of the bicipital sulcus as well as complete destruction and separation of its ends was encountered, sometimes with the formation of a new attachment of the distal tendon somewhere in the vicinity of the bicipital groove. These findings were attributed by Meyer to friction of long-continued overuse in the position of abduction and external rotation, and he wondered why "Such cases apparently do not appear in clinics and dispensaries, for pathologists and orthopedic surgeons seem to be unfamiliar with them." [9a] In a study of 150 routine specimens from the shoulders of cadavers Horwitz [10] confirmed Meyer's findings. He found flattening, fraying and fibrillation of the tendon in 30 instances. Four complete tears were noted. Subsequent to Meyer's studies, Gilcreest pursued a clinical investigation of the subject.[11] Gilcreest's observations covered 100 cases of rupture of the long biceps tendon. He recognized the clinical occurrence of a "latent" as well as an acute type, and stated that the former is generally unrecognized, or is diagnosed by the attending physician as sprain, arthritis, bursitis, etc. Gilcreest did not share Meyer's opinion that the condition was caused purely by attrition and spoke of senility, arthritis, myositis, arteriosclerosis, acute and chronic infections, neoplasms, physiologic predisposition, occupation, fatigue and trauma as possible causes.

That these changes in the tendon may represent the sequelae of tenosynovitis was apparently not considered by most writers on the subject, although Ewald [12] did suggest tenosynovitis as the cause of rupture of the long biceps tendon. In this country, tenosynovitis of the long biceps tendon has been vaguely referred to for many years. Codman recollected that he had heard the diagnosis made frequently when he was at medical school, but said that it was employed to describe a pain on moving the elbow up and down, a motion which plainly does not cause the biceps tendon to move. Codman doubted the existence of the lesion, saying that he had never demonstrated it clinically, at operation or at autopsy. At complete variance with this view is that of Pasteur [13] in France, who described a syndrome of pain and stiffness in the shoulder which he ascribed to *téno-bursite bicipitale,* a new entity. Pasteur did not believe the condition to be very common and expressed confidence in the response of the lesion to faradization. Several years later, Schrager [14] restated Pasteur's findings in what I believe to be the first report of tenosynovitis of the biceps tendon in the American literature. Full credit was given to Pasteur for the original description of the ailment. Schrager expressed the opinion that it was the most common cause of periarthralgias about the shoulder. Diathermy was considered to be almost specific therapy. Neither Pasteur nor Schrager had had opportunity to confirm the presence of the lesion either surgically or by autopsy. The evidence presented in this paper supports the major contention of both Pasteur and Schrager.

---

10. Horwitz, M. T.: Lesions of the Supraspinatus Tendon and Associated Structures, Arch. Surg. **38**:990 (June) 1939.

11. Gilcreest, E. L.: Rupture of Muscles and Tendons, J. A. M. A. **84**:1819-1822 (June 13) 1925; Subcutaneous Rupture of Long Head of Biceps Flexor Cubiti, S. Clin. North America **6**:547-554, 1926; Dislocation and Elongation of Long Head of Biceps Brachii, Ann. Surg. **104**:118-138, 1936.

12. Ewald: Bizepsriss und Unfall, München. med. Wchnschr. **74**:2214-2215, 1927.

13. Pasteur, F.: La téno-bursite bicipitale, J. de radiol. et d'électrol. **16**:419-426, 1932; Sur une forme nouvelle de périarthralgie et d'ankylose de l'épaule, ibid. **18**:327-328, 1934; Ténobursite bicipitale, Presse méd. **41**:142-143, 1933; La téno-bursite de la longue portion du biceps, Gaz. d. hôp. **107**:477-479, 1934.

14. Schrager, V. L.: Tenosynovitis of the Long Head of the Biceps Humeri, Surg., Gynec. & Obst. **66**:785-790, 1938.

PERIARTHRITIS CLINICALLY

Occurrence.—Periarthritis is in my experience the most common ailment of the shoulder. It is the most frequent, not only in private practice but also in the hospital outpatient department, an incidence which shows that neither the working nor the leisure class is spared. Records reveal its greater frequency in women (65 per cent) and its occurrence chiefly on the right side (72 per cent), the latter observation suggesting the predisposition of the shoulder getting the hardest usage. Two of 3 cases have occurred between the ages of 40 and 60, though the condition has been observed as early as the late twenties and as late as the early eighties. Worthy of comment is the not uncommon occurrence of "frozen shoulder" as a complication of pulmonary and cardiovascular disease, a fact which supports the contention that general debility or attrition may play a role in its etiology. The onset is generally insidious, but in about 1 of 3 cases a clearcut history of trauma is obtained.

Clinical Picture.—The typical history is that of a mild ache in the involved shoulder, often projected down the outer aspect of the upper part of the arm. In the beginning, pain is usually noted only at the limits of normal motion. Sometimes the condition is aborted at this stage after a few weeks and leaves no clinical sequelae. In other instances, this status may persist for months or even years without change and then clear up spontaneously. Generally, however, the pain slowly becomes more severe, and the arm stiffer, until the condition wears the patient down through interference with sleep. At first the limit of external rotation is painful. Progressively, as the pain increases, the entire range of motion of the shoulder shrinks, sometimes to such a point that the appearance of fibrous ankylosis is present. At times, a secondary scalenus spasm develops, and the misery of the patient is increased by pain in the neck and in the back of the shoulder. There may also be radiation of pain and tingling down the inner aspect of the arm to the fingers. I have seen the scalenus spasm so severe as to mask completely the pain in the shoulder, so that interpretation of the picture became apparent only during the examination, when restriction of motion was encountered. Occasionally, and possibly owing to the lack of sensitivity of the individual patient, pain is a negligible factor and the patient presents himself with no history of pain, complaining only of stiffness and restricted use of the involved extremity.

The illness pursues its inexorable undulant course, some days better, some days worse, until a point is reached when, inexplicably, the sequence just described reverses itself. The pain becomes more bearable, although no change is noted in the stiffness of the shoulder. Eventually, motion of the shoulder joint gradually improves and, with ups and downs, complete recovery ensues. Characteristic of the illness is the extreme and unpredictable variability of the time element and the curious static periods which may last for months during which neither improvement nor retrogression can be noted. Most patients are well before ten months have elapsed, though the duration of the illness may vary between three months and two and one-half years. I have never encountered a patient with symptoms of more than two and one-half years' duration, nor have I ever seen recurrent attacks in the same shoulder.

Examination.—The amount of pain and stiffness in the involved shoulder varies with the duration and severity of the illness. In early stages, or in mild forms of the disease, the range of motion may be entirely unrestricted, there being pain only at the limits of normal motion. On the other hand, so little motion may be detected in the shoulder that fibrous ankylosis is simulated. Generally, the patients are first seen at some point between these extremes. Characteristic of the late stages are

the freedom of motion and absence of pain when the shoulder is moved within the limits of its restricted arc. Only when these limits are forced does the typical excruciating pain manifest itself. As Schrager has pointed out, exquisite tenderness over the bicipital groove is invariably present, though the patient is generally surprised at the location of the tender area. I have found the following sign to be equally reliable. With the elbow actively flexed to a right angle so as to produce tension in the biceps mechanism, the thumb of the examiner identifies the long biceps tendon about 3 inches (6.6 cm.) below the joint. The structure is pushed gently to one side and then allowed to slip back to its normal position. As this occurs, a twinge of pain is felt in the involved bicipital groove. Yergason's sign [15] has not been found reliable, an observation which indicates that *motion* rather than *tension* of the tendon produces pain. In cases of long-standing disability, there is flattening of the shoulder because of deltoid atrophy, and the roentgenogram, which is otherwise normal, may show marked globular atrophy about the greater tuberosity, as well as spotty atrophy of the Sudeck type involving the entire humerus.

In the clinical examination, two important differences stand out between the pain due to periarthritis and that due to calcific deposits. I refer first to the absence of tenderness laterally over the insertion of the supraspinatus or infraspinatus muscles, and secondly, to fixation of the shoulder, not by painful spasm, but by a much less painful block suggesting mechanical obstruction.

MECHANISM

The long head of the biceps, like the appendix, is an unimportant vestigial structure unless something goes wrong with it. Its function as an abductor of the arm is certainly redundant, and sufficient evidence has accumulated to show that its role in holding the head of the humerus against the glenoid cavity is equally dispensable. A few aspects of relevant anatomy will help to clarify its potentialities as a handicap to function of the shoulder when it fails to operate normally.

The biceps "sheath" differs from a true sheath by being closed only at the lower end. It is therefore really a pouch or sac extruded from the shoulder joint. The lining of the joint extends down the bicipital sulcus for about 2 inches (5 cm.). At this point it reflects loosely onto the tendon itself and returns. It adheres to the tendon in its course through the bicipital groove and across the joint, as far as its insertion above the glenoid cavity. Although the cuff is tight where the tendon emerges from the cavity in the joint, the tendon glides freely through it, so that when the arm is in the position of full abduction, scarcely ½ inch (1.3 cm.) of tendon remains in the shoulder joint, the remainder being displaced into the groove. Since almost 2 inches (5 cm.) of tendon is in the shoulder joint proper when the arm is depressed and externally rotated, the excursion is a large one. These facts are important because they indicate that the movable tendon cannot properly be said to have two parts, an intracapsular section and a section enclosed by the bicipital groove (Gilcreest [11]). Moreover, because of the wide excursion of the tendon, it is clear that an inflammatory process originating in the bicipital groove will spread to some extent to the intra-articular tendon and immediate surrounding structures.

Another interesting point about the biceps tendon is that it does not slide in its sheath in response to pull of the muscle to which it is attached. The biceps muscle exerts its force essentially on motion of the elbow joint, and its long tendon,

15. Yergason, R. M.: Supination Sign, J. Bone & Joint Surg. **13**:160, 1931.

although tensed, remains immobile. Motion of the long biceps tendon with reference to the humerus is passive and occurs only when the shoulder joint is moved. These facts were studied in the cadaver and on the operating table, and the following salient phenomena were consistently revealed:

1. No motion of the biceps tendon in the bicipital groove can be produced by contraction or relaxation of the biceps muscle if the shoulder is held immobile in any position.
2. Conversely, any motion of the shoulder joint entails motion of the biceps tendon in the bicipital groove.
3. Elevation of the arm in internal rotation causes minimal excursion of the biceps tendon; in external rotation, maximum excursion.

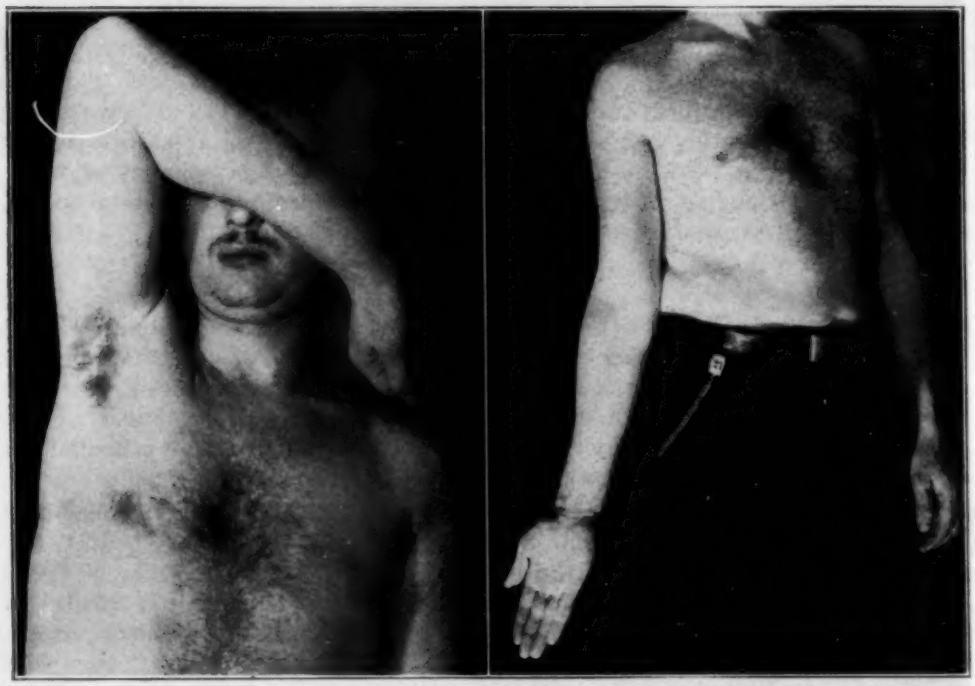

Fig. 1.—*A*, position of arm producing minimum length of intra-articular tendon. *B*, position of arm producing maximum length of intra-articular tendon.

4. The greatest excursion of the biceps tendon is produced when the following positions are alternated: (*a*) The tendon is drawn from above into the groove by elevation, internal rotation and forward flexion (fig. 1 *A*). (*b*) The tendon is drawn into the groove from below by backward flexion and external rotation with the arm depressed (fig. 1 *B*).

It is apparent from these data that if the extremes of motion of the biceps tendon in the bicipital groove are painful, motion of the shoulder will also be painful at the limits as noted. If all motion of the biceps tendon in the bicipital groove are painful, all movement of the shoulder will be equally so. Moreover, there is no reason why, under the circumstances, any interference with function of the elbow should occur.

SURGICAL INVESTIGATION

To determine whether tenosynovitis of the long biceps tendon was actually present in so-called "periarthritis," it was considered justifiable to subject a number of typical patients to surgical exploration. The operative procedure was standardized and was carefully carried out, so that no important structures of the periphery of the joint could be neglected.

Through a 2½ inch (6.5 cm.) incision splitting the deltoid muscle (fig. 2) the bursa was entered slightly lateral to the bicipital sulcus and inspected for adhesions

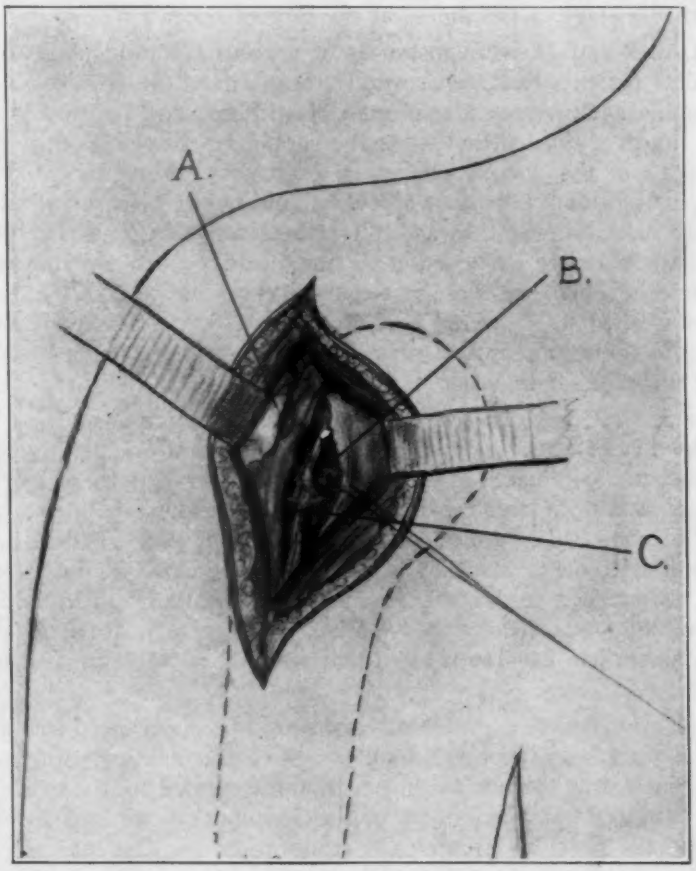

Fig. 2.—Typical appearance of involved structures in severe "frozen shoulder": *A*, glistening, normal-appearing subacromial bursa; *B*, thickened, edematous tendon sheath; *C*, adherent, frayed and roughened long biceps tendon.

and other inflammatory changes. By inward rotation of the humerus, the floor of the bursa and the underlying musculotendinous cuff were inspected. The arm was then rolled back to neutral position to bring the bicipital sulcus into the wound, and in its lower portion a half-inch (1.3 cm.) nick was made in the sheath, exposing the tendon. Flexion and extension of the shoulder were then cautiously performed through the unrestricted arc and the tendon inspected for motion in its sheath. The sheath was then completely split open through the intratuberous notch, to expose the tendon as far as its entrance into the joint proper. Again the shoulder was gently moved while the tendon was observed to determine its

freedom of motion. If the tendon did not move when inspected through the slit but was free when the sheath had been completely opened, the restriction was considered referable to stenosis, such as is encountered in de Quervain's disease, and not to adhesions. Sections of tendon sheath were then excised for microscopic study. The subsequent procedure will be described hereinafter.

The pathologic conditions encountered in 12 shoulders explored according to the plan just outlined are presented in the accompanying table.

Gross Findings.—Noteworthy was the universal finding of tenosynovitis involving the long biceps tendon, the character and extent of involvement corresponding roughly with the stage of the illness at the time of operation.

Cases 1, 2, 9 and 11 were instances of a relatively mild phase of the illness. Although all 4 patients had been severely incapacitated by pain for a long period, clinical examination revealed a minimum of stiffness, and pain could be produced only at the limits of normal motion of the shoulder. Exploration of the shoulders disclosed in all of them some restriction of motion of the biceps tendon in the groove. Although filmy adhesions were encountered in 1 (case 1), all the tendons moved freely once the sheath was split open completely, and the limitation was accordingly attributed to constriction of the sheath. Gross inflammatory changes were encountered, but they were not extensive. Microscopically, sections of the tendon sheath failed to show the hyaline changes that characterize de Quervain's disease but did show inflammatory changes which differed in no essential manner from those encountered in other explorations.

In cases 5, 6, 7, and 12 the disease was clinically more severe than in the aforementioned cases. Moderate stiffness was present on preoperative examination, but the picture was dominated by excruciating pain and tenderness over the bicipital sulcus. Exploration in these patients disclosed tendons bound down to their sheaths with many thick adhesions. The sheaths were reddened, edematous, thickened and extremely vascular. The tendons themselves appeared dull and discolored. Roughness and some fraying were encountered in 3 cases. In 1 (case 5) free fluid was encountered in the sheath, and in another (case 12) the gliding mechanism had been so injured that tendon and sheath constituted a single swollen mass.

Cases 3, 4, and 10 were representative of a still more advanced lesion. Although the patients had all been through a long period of excruciating pain, at the time of operation stiffness was the outstanding symptom revealed by the examination, and neither the pain nor the tenderness in the bicipital groove was as severe as in the patients in the previous group. On exploration, these shoulders revealed less gross evidence of inflammation than characterized the preceding group. Although some vascularity and edema were encountered, the picture was predominantly that of thick, heavy fibrosis. The sheaths were thickened and fibrotic, and the tendons were firmly glued to them with strong adhesions. When freed from surrounding adhesions, the surfaces of the tendons were irregular, roughened, frayed and fibrillated. Patient 8 showed the most advanced changes encountered in the entire series, and it is unfortunate that the history obtained was not a reliable one. Preoperative examination revealed free passive motion, but weakness of active abduction. Tenderness of the biceps muscle and the biceps sign were present. Exploration revealed thickening and adhesions in the subacromial bursa and a complete tear of the musculotendinous cuff. The biceps tendon had become firmly attached to the bicipital groove, and its intra-articular section had completely disappeared except for a small stub remaining attached to the glenoid tubercle.

Summary of Data on Twelve Patients Submitted to Operation

Case; Name; Age	Sex; Date; Side	Duration	Trauma	Symptoms and Signs: Pain	Stiffness	Tenderness Over Bicipital Groove	Biceps Sign	Secondary Scalene	Roentgenogram	Gross Operative Findings: Bursa	Musculotendinous Cuff	Temosynovitis	Tendon "Frozen" to Sheath	Appearance of Tendon	Appearance of Tendon Sheath
1 J. de la F. 28	M May 1940 R	1 year	Injury	At normal limits	0	++	++	0	Negative	Negative	Negative	++	Limited motion	Dull, reddened; light adhesions	Thickened, slight edema; no increased vascularity
2 D. P. 29	M Aug. 1940 R	2 years	Injury	At normal limits	0	++	++	0	Negative	Negative	Negative	+	Slight motion	Dull, reddened, thinned	Marked thickening and fibrosis; vascularity not increased
3 J. de S. 36	M Aug. 1940 L	6 months	Chronic	+	++	++	++	0	Negative	Reddening; local adhesions	Negative	+++	Limited motion	Thinned, dulled	Moderate thickening and fibrosis; some edema
4 R. S. 54	M Nov. 1940 R	6 months	Heavy labor	+−	+++	++	++	+	Moderate atrophy	Slight thickening	Negative	+++	+	Rough, frayed, firmly adherent	Slightly increased vascularity; marked thickening and fibrosis; no edema
5 J. R. 33	M Dec. 1940 L	4 months	Chronic	+	++	++	++	+	Moderate atrophy	Thickened, reddened	Negative	+++	+	Rough, frayed, adherent	Vascular, thickened and edematous; fluid in sheath
6 H. C. 59	M March 1941 L	10 months	Chronic	+++	++	+++	++	0	Marked atrophy	Local adhesions	Negative	+++	+	Dulled, roughened, thinned	Extremely vascular; markedly thickened and edematous
7 H. C. 59	M March 1941 R	2 months	Chronic	+++	+	++	++	+++	Negative	Local adhesions	Negative	+++	+	Reddened, dulled, frayed	Extremely vascular; markedly reddened, thickened and swollen
8 P. I. 56	M Oct. 1942 R	4 months	Heavy lifting	+	+−	++	++	0	Marked atrophy	Adherent	Complete tear	+++	+	Could not be separated from sheath; disintegrated above groove	Sheath and tendon bound down in large inflammatory adherent mass
9 M. M. 32	F Aug. 1942 R	1 month	Injury	At normal limits	0	++	++	0	Negative	Negative	Negative	+	+	Rough, red, compressed	Slight thickening and increased vascularity
10 A. B. 54	F Oct. 1942 R	9 months	Chronic	++	+++	++	++	0	Marked atrophy	Locally inflamed	Negative	+++	+	Roughened, frayed; many adhesions	Edema and marked hypervascularity and thickening
11 J. S. 46	M Nov. 1942 L	2 months	Chronic	++	0	++	++	0	Slight atrophy	Negative	Negative	+++	Moderate motion	Roughened, edematous; covered with granulation tissue	Marked thickening; many adhesions; fluid in sheaths; edema
12 R. K. 51	F Dec. 1942 L	6 months	Chronic	++	+++	++	++	+	.....	Negative	Negative	+++	+	Firmly bound to sheath; edematous	Vascular, thickened and bound to tendon in an indistinguishable mass

Microscopic Appearance.—In almost all of the aforementioned cases, sections of the tendon sheath were removed and subjected to microscopic examination. The changes exhibited in these sections were essentially so uniform that they may be considered together. Inflammatory infiltration, increased vascularity and advanced hyperplasia characterized all of them. Spotty areas of leukocytic and lymphocytic infiltration were common, as well as edema, infiltration into the blood vessels, synovial degeneration and degeneration of collagen fibers. Proliferative changes, present in all specimens, were predominant when the disease was well advanced. Heaping up of the synovial elements and fibroplastic activity were noticeable. In only 1 instance (case 3) was hyaline degeneration noted suggestive of the picture described by de Quervain as characteristic of tendovaginitis at the radial styloid. For obvious reasons, sections of tendon proper were not obtained.

Summary of Observations at Operation.—Pathologic study of these 12 cases of periarthritis showed that tenosynovitis of the long biceps tendon was present in all. In only 1 instance was a rupture of the musculotendinous cuff encountered, and in no case was any significant change encountered in the subacromial bursa or other periarticular tissues. Only two interpretations of these data appear plausible. Tenosynovitis of the long biceps tendon can represent either an extremely common incidental finding or a basic element of the disease. The normal-appearing and mobile tendons encountered in the course of numerous explorations preparatory to the Nicola and related procedures indicate that the former possibility may be excluded. It is therefore reasonable to infer that tenosynovitis of the long biceps tendon constitutes the underlying pathologic basis of at least most cases of so-called periarthritis.

COMMENT

The demonstration of tenosynovitis as a consistent finding in so many frozen shoulders brings up a few points for discussion. In the first place, these surgical experiments have shown the term periarthritis, at least in the sense in which it was used by Duplay, to be inaccurate. The term "frozen shoulder" remains applicable only to the more severe forms. Accordingly, it is proposed that the pathologically descriptive name bicipital tenosynovitis be employed for the condition.

Perhaps of greater importance is the insight gained from this study into the pathologic mechanism which accounts for the inevitable spontaneous clinical recovery. When the operative findings are arranged in the order of the severity of the preoperative clinical picture, it becomes evident that the inflamed biceps tendon becomes more and more adherent to its sheath until it is solidly anchored to it. The inflammatory reaction, extensive while the tendon is still mobile, gradually subsides and finally disappears as the fixation of the tendon to the surrounding tissues becomes firm. It is worthy of note that in the later stages of the disease almost complete fixation and diminishing inflammation were observed before the termination of the period of increase in the severity of symptoms, to which our surgical investigations were necessarily confined. Solid anchorage of the tendon to the bicipital groove, therefore, may be assumed to coincide roughly with the clinical stage at which pain subsides and motion of the shoulder commences to improve. In other words, spontaneous improvement begins when solid and painless fixation of the tendon to its sheath has been achieved.

No opportunity to observe subsequent pathologic changes was presented in these cases, but the previously described postmortem material of both Meyer and Horwitz contained specimens which no doubt represented sequelae of this condition. These specimens indicated that fixation of the tendon to the lesser tuberosity

remains permanently, and this contention is supported clinically by the fact that recurrences of frozen shoulder are not encountered. Moreover, it appears that the intra-articular section of the tendon, no longer useful, becomes attenuated and finally disintegrates. In Horwitz' 4 examples of complete tear the distal portion of each tendon was found attached to the lesser tuberosity. The proximal tendon in 1 had completely disappeared. In 2, only a small stub remained attached to the glenoid tubercle and in the fourth, the proximal portion had become attached to the articular surface of the humerus.

In résumé, then, it is possible to reconstruct the pathologic sequence underlying typical frozen shoulder as follows: The condition is initiated by a mild tenosynovitis gradually becoming more severe, and with adhesions which become more and more firm. During this process, the shoulder becomes progressively stiffer. Once the adhesions become sufficiently solid to anchor the tendon firmly at the intertuberous groove, pain diminishes and increased motion of the shoulder commences. Return of normal function in the shoulder coincides with the subsidence of inflammatory reaction, which is followed by disintegration of the intra-articular tendon.

It has been stated that the mechanism described refers to "typical" frozen shoulder. Every tenosynovitis of the biceps tendon does not pursue this typical clinical or pathologic course. That the process may be aborted at an early stage is indicated clinically by mild attacks of very short duration which are prone to recurrence, and pathologically by a frayed and fibrillated but nonadherent tendon, also described by both Meyer and Horwitz as commonly observed at postmortem examination.

The exact mechanism by which tenosynovitis of the long biceps tendon produces restriction of motion in the shoulder has presented a perplexing problem. It is plain that when the tendon is frozen to the humerus in neutral position, adduction and external rotation at the shoulder should be limited by tension of the intra-articular tendon itself. Elevation and internal rotation, however, should relax intra-articular tendon, and since these motions are blocked in "frozen shoulder," the cause of the block must be sought elsewhere. The explanations that suggest themselves may be listed as follows:

1. Adhesive subacromial bursitis.
2. Contracture resulting from long-standing voluntary immobilization.
3. Mechanical block caused by infolding of redundant intra-articular tendinous extension.
4. Peritendinous adhesions extending upward into the joint, binding the tendon to the capsule and musculotendinous cuff above and to the articular surface of the humerus below.

Although in the past frozen shoulder has been attributed to adhesive subacromial bursitis, this condition was encountered only once among the 12 patients who were operated on. Apart from occasional insignificant adhesions in the vicinity of the bicipital sulcus, the subacromial bursae in the 11 other patients were normal in appearance. This hypothesis, therefore, is untenable and may be discarded. The theory that a true contracture of the joint results from long-standing immobilization is not reconcilable with my experience in the operating room. In the frozen shoulders operated on, resistance to shoulder abduction persisted until the peritendinous adhesions were freed. As soon as this was accomplished, full motion of the shoulder was possible without forcing and with only the slightest palpable resistance. These observations are incompatible with a generalized contracture at

the joint and indicate rather a localized mechanical block in the immediate vicinity of the area of tenosynovitis. Two possible hypotheses appear compatible with these findings. The first is that the adhesions of the tendon to the sulcus cause the intracapsular portion to buckle downward when the arm is abducted. In this manner, a mechanical block is established similar to that caused by a displaced meniscus in the knee. Surgical release of the adhesions permits the tendon to slide down in its groove when the arm is abducted or internally rotated so that the block disappears. This hypothesis was proved incorrect by the following experiment: After the tendon had been liberated from the groove and the return of normal motion in the shoulder joint had been demonstrated, resuture of the tendon to the groove was performed. No block to motion of the shoulder reappeared. It seems, therefore, that stiffness of the arm is most reasonably attributable to the other possibility, namely, an upward extension of the tenosynovitis into the joint, so that the intra-articular tendon is "frozen" to the capsule above and to the articular surface of the humerus below. Adhesions in these locations might well account for mechanical fixation of the shoulder, since the tendon runs oblique to the supraspinatus and infraspinatus muscles. The occurrence of such adhesions is not surprising when it is recalled that the upper end of the sheath is patent and that in periarthritis the inflamed tendon glides freely into the joint proper. The limitations of my surgical exposure precluded visualization of such a block, and an exposure extensive enough for this purpose was considered inexpedient; but the foregoing data allow of no apparent alternative explanation. Snaps audible during brisement forcé, then, would appear to represent tears either of intra-articular peritendinous adhesions or perhaps of the attenuated intra-articular tendon itself.

THERAPY

Recognition of the pathologic sequence underlying periarthritis provides a guide for the reasonable administration of conservative therapy and suggests also a surgical method for its radical cure. In any consideration of therapy, it is of prime importance to bear in mind the inevitable favorable prognosis of the illness, even when no therapy whatever is administered. The many conservative measures that have been advocated for the treatment of this condition are well covered in the literature of the past three decades (see Codman bibliography [16]), and a review of this material is beyond the scope of the present paper. The nature and sequence of the underlying pathologic changes indicate, however, that therapeutic measures must be properly timed if the natural healing processes are to be expedited and not delayed by them. In the early stages, it would seem that too much stress has been laid on electrotherapeusis and insufficient attention paid to rest and immobilization, preferably in the position of abduction. According to my experience with tenosynovitis elsewhere, rest not only relieves pain but sometimes aborts the condition. When the tenosynovitis is too far advanced to permit one to anticipate the latter eventuality, immobilization permits adhesions to form about the tendon without the retardation and pain caused by continual motion. As for manipulation, this procedure is clearly useless before stiffness becomes noticeable, and harmful during the period when adhesions are forming and stiffness is becoming progressively more severe. At this time, manipulation either under anesthesia or gently by exercises serves only to increase pain and disrupt soft adhesions, which inevitably reform. These theoretic considerations have been repeatedly confirmed in clinical practice.

16. Codman,[8] pp. 211-213.

In the upgrade or healing stage, when stiffness is subsiding, almost any therapeutic procedure will receive unwarranted credit. During this period manipulation, either with the patient under anesthesia or by repeated gentle stretching, does appear to hasten the return of normal motion, though this is difficult to prove. It seems likely that at this stage the attachments of the tendon to the groove are so strong that they are no longer jeopardized and only intra-articular adhesions, or the tendon itself, are stretched or torn.

Surgical therapy is indicated (general condition of the patient permitting) at any stage of the illness when the condition has remained static for a long period, when progress is unduly slow, or when, for extraneous reasons, a more rapid recovery is desirable. The common concomitance of this condition with preexisting or impending cardiac disease suggests caution in excluding these ailments before operation is advised.

Mention has already been made of the cases of protracted involvement in which stiffness remains in abeyance and in which pain is elicited only at the extremes of normal motion. Exploration in 3 such cases revealed tendons fixed to the sheath, not by adhesions but by constricting tendovaginitis, as in de Quervain's disease. In these cases, release of the constriction provides room for the tendon to resume its normal motion in the groove at the operating table. While this condition does not conform to de Quervain's description of the characteristic histologic picture of tendovaginitis, it would appear that it may be clinically regarded as such, and so treated. Simple release of the constriction followed by loose resuture of the sheath in several cases resulted in prompt cessation of pain as well as in rapid and lasting recovery.

For patients with intractable pain and stiffness, i. e., the typical frozen shoulder, the objectives of surgical therapy is the obliteration of the involved tendon—tendon sheath mechanism. This may be accomplished by one of several procedures that have been described and accepted for other purposes. Of these procedures, the Nicola operation and transplantation of the long head of the biceps to the short head or coracoid process may be utilized but are not recommended. Both operations are more extensive than is necessary and entail a relatively long convalescence. I favor suture of the long head of the biceps to the lesser tuberosity, with the arm in adduction and external rotation. This position insures that the intra-articular tendon will be long enough to permit full external rotation. If the tendon is sutured to the tuberosity with the arm in internal rotation, the shortened structure itself will limit full motion of the shoulder. Through a 2 inch (5 cm.) incision splitting the deltoid muscle the long biceps tendon is freed from the surrounding thickened sheath until it moves freely as the shoulder is moved, hypertrophied sheath being freely excised. With the arm in adduction and moderate external rotation, several firm silk sutures are inserted to anchor the tendon to the lesser tuberosity. A uterine clamp or a towel clip may be useful for perforating the latter structure for this purpose. One or two sutures are then placed at a higher level, so as to anchor the tendon to the soft tissue. These sutures prevent play of the tendon when the arm is rotated. Closure is accomplished in layers, and a Velpeau bandage is employed for several days. Detailed experience in the use of this operation for the treatment of frozen shoulder will constitute the subject of a separate report. Suffice it here to say that pain is almost immediately alleviated, that improvement in motion of the shoulder commences promptly, and that activity may generally be resumed in four to six weeks.

SUMMARY AND CONCLUSION

Periarthritis, or frozen shoulder, is a common disabling illness from which recovery is spontaneous, though its course is protracted and its duration unpredictable. Theoretic considerations have suggested that the basic pathologic condition is a tenosynovitis of the long head of the biceps and its sheath. Surgical exploration in 12 cases showed that this lesion was present in all instances, and that no other pathologic lesion of the periarticular structures was consistently present. These findings indicate that bicipital tenosynovitis is the pathologic basis of periarthritis in at least the majority of instances.

Further studies of the result of these surgical explorations indicate that in typical cases the tenosynovitis is adhesive and results in firm fusion of the tendon with the structures of the bicipital groove. When fusion becomes solid, inflammation subsides. Correlation of this picture with the clinical observations in the cases in which exploration was done indicates that clinical improvement commences as soon as the tendon is firmly fused to the humerus. The reports of other workers on material obtained at autopsy suggest that disintegration of the intra-articular portion of the tendon may follow in the period after firm adhesions have developed. This sequence of pathologic events explains how spontaneous cure occurs and why recurrences fail to develop.

The mechanism by which adhesive tenosynovitis produces a frozen shoulder is discussed and various possible explanations evaluated. These studies have cast no light on the basic cause of the condition or on the reason for its frequent concomitance with cardiac and pulmonary disease.

On the basis of the pathologic picture and sequence underlying the illness, the merits and timing of conservative therapy are discussed, and a surgical procedure is described for the radical treatment of the condition when rapid cure is desired.

Dr. Paul Klemperer was responsible for the interpretation of the microscopic material.

910 Park Avenue.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

I. CONGENITAL DEFORMITIES

PREPARED BY DR. J. HIRAM KITE, ATLANTA, GA.

Experimental.—The section on congenital deformities in "Progress in Orthopedic Surgery for 1941" opened with an account of Warkany's work on the production of skeletal abnormalities in the offspring of rats fed on a deficient diet. During 1942 he and his associates have reported further on the same work. They [1] point out that it has been asserted often that faulty nutrition of the fetus may be a cause of congenital malformations. The faulty nutrition may have its origin in various disturbances. Faulty implantation of the ovum, diseases of the placenta, interruption of the umbilical blood flow, toxic substances transmitted through the placenta and deficiencies in the diet of the mother have been suggested as causes of deformities in the mammalian embryo or fetus. The last-mentioned cause has aroused new interest in recent years. Warkany and Nelson give the following summary of the work:

1. Skeletal abnormalities occurred in about one third of the offspring of female rats reared and bred on Steenbock and Black's rachitogenic diet no. 2965 supplemented with viosterol (diet I).
2. Similar skeletal defects were not found in the offspring of females of the same strain reared and bred on a stock diet.
3. Similarly no such defects were observed in the offspring of females of the same strain reared and bred on diet II, a diet which differs from diet I in that it contains 2 per cent dried pig liver and only 1 per cent of calcium carbonate.
4. The defects were also absent in the offspring of females reared and bred on diet I supplemented by 2 per cent pig liver only (diet VI).
5. If in diet I the calcium carbonate content was reduced from 3 to 1 per cent, only about one tenth of the offspring showed abnormalities of the pattern of diet I.
6. By alternately breeding the same female on diets I and II, abnormal and normal litters could be produced alternately.
7. The same pattern of abnormalities was obtained in the offspring of rats of two different strains reared and bred on diet I.
8. Apparently a nutritional factor that is absent or inadequate in diet I and present in liver in large amounts is necessary for the normal intrauterine development of the rat.

The frequency of osseous defects in 100 cleared abnormal specimens was found to be as follows [2]:

Tibia	93	Ulna	50
Mandible	80	Humerus	34
Ribs	75	Hindfoot	31
Fibula	63	Maxilla	8
Radius	58	Scapula	6
Hand	54	Clavicle	6
Sternum	52	Femur	1

A histologic study [3] was made of some of the previously described skeletal abnormalities in the offspring of female rats reared on a deficient diet. The

1. Warkany, J., and Nelson, R. C.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency, J. Nutrition **23**:321-333 (April) 1942.
2. Warkany, J., and Nelson, R. C.: Experimental Production of Congenital Skeletal Abnormalities in Offspring of Rats Fed Deficient Diet, Am. J. Roentgenol. **47**:889-892 (June) 1942.
3. Warkany, J.: Skeletal Abnormalities Induced in Rats by Maternal Nutritional Deficiency: Histologic Studies, Arch. Path. **34**:375-384 (Aug.) 1942.

abnormal structures examined showed more or less delay in ossification. The orderly relationship between the calcifying cartilage and the osseous parts of the bones was definitely disturbed. Persistence of cartilage was found in areas where ossification should have taken place. The cartilage itself showed signs of abnormal development. The outlines of the structures affected were abnormal in the cartilaginous stage. In early stages of development centers of calcification seen in atypical places explained the abnormal arrangement of the osseous trabeculae found in later stages. It is suggested that a nutritional factor absent in the deficient diet but present in large amounts in liver is necessary for the normal prenatal development of bone in these rats.

Warkany and his associates tried varied diets on different strains of rats [4] and showed that the addition of iodine, manganese, casein, alfalfa leaf meal and cod liver oil to the diet of females on diet no. I did not prevent abnormalities. The addition of 2 per cent of dried pig liver or of an amount of alcoholic extract of liver equivalent to 4 Gm. for each hundred grams of diet I did prevent all abnormalities. Another series of experiments was carried out to determine the embryologic period in which the malformations are determined. The gestation period of the rat is twenty-two days. Addition of liver before the fourteenth day prevented abnormalities, while after the fourteenth day some abnormalities appeared. This same diet was again tried on three different strains of rats. Two strains survived and one died out on it. The strain which died out produced only 1 offspring, and it was normal. Warkany and his associates believe these observations might be used to refute the conclusion that a given stock is always biologically inferior when congenital malformations appear. In fact, the results of breeding these different strains of rats under adverse environmental conditions indicate that the appearance of malformed offspring rather than none at all may be a sign of hardiness and vigor.

Ehlers-Danlos Syndrome.—Another report appeared in 1942 on the Ehlers-Danlos syndrome. Gordon [5] reports the case of a 46 year old housemaid who was troubled with splitting of the skin after mild injuries. She and other members of her family were bleeders. Examination of her blood revealed that the bleeding and the clotting time and the number of platelets were normal. There was hyperextensibility of the thumbs of each hand, and the skin was hyperelastic over the elbows. There were numerous linear scars on the subcutaneous surfaces of both ulnas, extending from the wrists to the elbows. Weber, who had reported earlier cases, discusses this one and expresses the opinion that it is a genuine case of Ehlers-Danlos syndrome, though the three main features were present in only a minor degree. He thinks it is interesting to know that this developmental dysplasia may be present in persons who can be regarded as almost normal. [ED. NOTE: A full discussion of the Ehlers-Danlos syndrome appeared in "Progress in Orthopedic Surgery for 1941." [6]]

Surgical Treatment.—Mowlem [7] discusses the surgical treatment of various congenital defects, only a few of which are of orthopedic interest. He suggests that syndactyly and polydactyly are best operated on between the second and the fourth year. The small raised hemangiomas with capillaries on the surface, which appear

4. Warkany, J.; Nelson, R. C., and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency: Use of Varied Diets and of Different Strains of Rats, Am. J. Dis. Child. **64**:860-866 (Nov.) 1942.

5. Gordon, H.: Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **35**:263-264 (Feb.) 1942.

6. Progress in Orthopedic Surgery: III. Congenital Deformities, Arch. Surg. **45**:653-667 (Oct.) 1942.

7. Mowlem, R.: Surgical Treatment of Congenital Defects, Proc. Roy. Soc. Med. **35**:683-684 (Aug.) 1942.

after birth are liable to spontaneous cure. Hemangiomas of the deep-seated, truly cavernous type require treatment with roentgen rays or radium.

Absence of Extremities and Bones.—Killingsworth and Engledow [8] report the case of a 3 year old child with congenital absence of the four extremities. Ectromelia of the four extremities is one of the rarest of human congenital anomalies. Only 3 cases have been reported in medical literature.

> The most plausible explanation of such a phenomenon, in view of the embryology of the human fetus, would seem to be that it is due to defective genes in either or both parents at the time of conception. All one can be certain of is that some pathologic or chemical change occurred at the 5 mm. stage of the fetus, thus preventing the normal development of the future limb buds.

Intrauterine amputations and constriction bands are discussed by Barenberg and Greenberg,[9] who report a case in which there was anesthesia below the constriction band. They think that the depth of the band on the right leg produced anesthesia. Frequent infections and ulcers, which responded poorly to the usual forms of treatment, were complicating factors. Excision of the constricting ring has been partly successful in restoring the function of the superficial nerves. The prevailing theories of the formation of these bands and amputations are briefly reviewed. The most tenable explanation assumes a localized primary defect in the germ plasm. An instance is cited in which amniotic adhesions produced constricting rings.

Complete absence of the posterior arch of the atlas is reported by Brown,[10] who states:

> The atlas here described is completely deficient as to the posterior arch. In the absence of the posterior tubercle of the atlas, the rectus capitis posterior minor muscles had their origin from an unusual bony prominence on the spinous process of the epistropheus. It is difficult to conceive that the substitute attachment of the minor rectus muscles to a more distant bone than is normal would have followed resorption of portions of the arch. Hence, this prominence may represent the posterior tubercle of the atlas, ossified from a separate center and united with the epistropheus.
>
> In the absence of evidence of pathology, and considering the substitute attachment of the muscles named, the interpretation of this specimen as a developmental anomaly seems to be the acceptable one.

Weiler [11] reports a case of congenital absence of the odontoid process of the axis. He says that dislocation of the atlas on the axis, complicated by congenital absence of the odontoid process of the axis, should be treated by reduction and operative fusion of these two cervical vertebrae, in order to prevent the damage to the spinal cord which would result from recurrent dislocation. He reduced the dislocation by traction and manipulation and obtained fusion by using a short section of rib, which was split longitudinally and sutured to the first and second cervical vertebrae. Two years have passed since the operation, and active use of the head and neck has caused no further complications.

Total congenital absence of the tibia is said to be the rarest of congenital deformities. A thorough search of the literature revealed only 89 cases. Nutt and

8. Killingsworth, W. P., and Engledow, R.: Congenital Absence of Four Extremities, Am. J. Dis. Child. **63**:914-918 (May) 1942.

9. Barenberg, L. H., and Greenberg, B.: Intrauterine Amputations and Constricting Bands: Report of Case with Anesthesia Below Constriction, Am. J. Dis. Child. **64**:87-92 (July) 1942.

10. Brown, C. E.: Complete Absence of the Posterior Arch of the Atlas, Anat. Rec. **81**:499-503 (Dec. 26) 1941.

11. Weiler, H. G.: Congenital Absence of Odontoid Process of Axis with Atlanto-Axial Dislocation, J. Bone & Joint Surg. **24**:161-165 (Jan.) 1942.

Smith [12] report a case of their own and give a follow-up report on Myers' case nearly thirty-five years after treatment. Their patient showed complete congenital absence of the right tibia, with no evidence of primary centers of ossification of the proximal end, of the tibial tuberosity or of the medial malleolus. The fibula was hypertrophied, shorter than normal and straight. The proximal end was displaced posteriorly and the distal end laterally from the astragalus. Attempts were made to place the fibula under the femur and over the astragalus by manipulation and casts, and later by operation when the patient was a year old. The fibula could not be held in the desired position, and when he was 5½ years old another operation was done. The leg was still in casts when the report was written. Myers' patient was able to walk with a long leg brace and thought that he had less trouble with his brace than some friends had with artificial limbs. [ED. NOTE.—Their roentgenograms made at the age of 5 show a center of ossification in the position of the proximal end of the tibia. In patients with congenital deformities, since the centers of ossification develop late, neither the tibia nor the fibula should be considered as totally absent until the patient is past 5 years of age.]

Multiple Anomalies.—Furst and Ostrum [13] report an unusual case, in which there was simultaneous occurrence of three rare developmental anomalies. This patient had platybasia, synostosis of the neck (Klippel-Feil syndrome) and Sprengel's deformity. They state that a common congenital etiologic relation is probable.

Clubbing of the Fingers and Toes.—Clubbing of the fingers and toes has been recognized since the time of Hippocrates as a manifestation of certain forms of intrathoracic disease. Thomas [14] reports a case of clubbing of the digits of unknown cause, but probably of congenital and familial origin. This case represents a borderline situation between acropachy and chronic osteoarthropathy.

Macrodactyly and Peripheral Nerves.—Moore [15] reports 5 cases of macrodactyly, in all of which pathologic changes were found in the peripheral nerves. In 1 (a young adult) the changes were definitely due to a neurofibroma. In the 4 others (all young children) the changes were an increase in endoneurial fibrous tissue, with evidence of degenerative changes in nerve fibers. Three of the 4 children showed at least some of the clinical stigmas of neurofibromatosis. It would seem, then, that the changes in the peripheral nerves may represent an early stage in the development of a neurofibroma.

The fact that local hypertrophy is so constantly associated with pathologic changes in the peripheral nerves would seem to indicate that there is a relationship between them. It is believed that the nervous system exerts some controlling action on the process of growth and that the impaired nerves fail in this function, so that uncontrolled or uninhibited growth results. Whether there are changes in the central nervous system which result in the change in the peripheral nerves is not known.

These observations seem to favor the neurogenic theory as the origin of at least certain types of congenital deformities. Moore feels that the investigation of disease

12. Nutt, J. J., and Smith, E. E.: Total Congenital Absence of Tibia, Am. J. Roentgenol. **46**:841-849 (Dec.) 1941.

13. Furst, W., and Ostrum, H. W.: Platybasia, Klippel-Feil Syndrome and Sprengel's Deformity, Am. J. Roentgenol. **47**:588-590 (April) 1942.

14. Thomas, H. B.: Agnogenic Congenital Clubbing of Fingers and Toes, Am. J. M. Sc. **203**:241-246 (Feb.) 1942.

15. Moore, B. H.: Macrodactyly and Associated Peripheral Nerve Changes, J. Bone & Joint Surg. **24**:617-631 (July) 1942.

of the peripheral nerves has been somewhat overlooked and that more careful work along this line might be of great interest.

Cystic Osteodystrophy.—A case of congenital localized cystic juvenile osteodystrophy is reported by Adler [16] in a male infant 4 weeks old in whom there had been demonstrated at birth a fracture of the right tibia and fibula, with callus formation, pseudarthrosis and cystic spaces. After six months the process had extended to the hitherto normal fibula of the left leg, with the same picture of cystic spaces in the vicinity of the fracture and pseudarthrotic healing with osteoporosis of the whole bone. The left tibia appeared roentgenologically intact. In the congenitally diseased right tibia and fibula the destruction of normal bone had extended farther, but not by contiguity. Above the described focus a similar one with the same roentgenologic aspect had appeared. Thus far there had been no spontaneous fracture, but there was renewed medullary hemorrhage. This case, then, was one of so-called localized cystic juvenile congenital osteodystrophy with development of pseudarthrosis, in which, in contradistinction to observations reported in the American literature, the process involved not only the tibia but the right and the left fibula as well.

Clubfoot.—Thomson [17] urges the use of Denis Browne splint for the treatment of congenital clubfeet. He has treated 60 patients in two and a half years, and had only 1 recurrence, and that was the fault of the parents, who abandoned the care of the feet. He prefers to start treatment during the first month of life, usually at about 3 weeks of age. The oldest untreated patient was 1 year of age. Thomson gives the following outline of his method:

> The principle of treatment for the correction of deformity is to strap the feet to the splint, which has a connecting cross bar, and then let the infant correct its deformity by incessant kicking. For the sake of convenience, the treatment is divided into four phases (assuming that it is started during the first few weeks of life):
>
> (1) The phase during which the deformity is corrected and carried into over-correction (usually five to six weeks' duration).
>
> (2) The phase of maintaining the correction in the same adhesive splints (approximately five months or even less, if the feet are large enough).
>
> (3) A further period of maintaining correction by the use of boot splints (about six months' duration or until walking commences).
>
> (4) The period during which the boot splints are used as night and resting splints, and supplemented with special walking boots during the active periods of the day. The duration of this phase will have to be decided upon in the future, but should be carried on for at least two to three years.

[ED. NOTE.—After having treated personally about 500 clubfooted children in the last nineteen years, I (J. H. K.) was very anxious to try a method which gave only 1 recurrence in 60 cases, and this the fault of the parents. With casts and wedgings I have not been able to get the percentage of recurrences below 10 to 15 per cent. After I had seen the method demonstrated by Dr. Thomson I obtained all three sizes of splints and tried it on 5 young clubfooted babies. At first it seemed to be an answer to a busy surgeon's prayer. Attention was given to every possible detail, in an effort to get the results claimed, but these could not be obtained. I was unable to correct all of the forefoot adduction. Fastening the feet to the cross bar in an outwardly rotated position caused an outward rotation of the entire leg. As the child attempted to rotate the leg inward to resist this, there was some twisting in the knee joint and in the ankle joint. The splint rotated the astragalus

16. Adler, K. J.: Congenital Localized Cystic Juvenile Osteodystrophy, Röntgenpraxis **13**:258-262 (July) 1941.

17. Thomson, S. A.: Treatment of Congenital Talipes Equinovarus with Modification of Denis Browne Method and Splint, J. Bone & Joint Surg. **24**:291-298 (April) 1942.

outward from under the tibia as far as the mortice beween the malleoli would permit. The first deformity in the clubfoot to be corrected is the forefoot adduction. This deformity occurs between the forefoot and posterior foot, chiefly in the midtarsal joint. This deformity may be slightly corrected as the foot is strapped to the metal splint, but no further correction can be obtained by rotating the splint outward.

When the cross bar is bent to force the feet up in dorsiflexion, they are brought up in too much valgus, and bad flatfeet are produced. With casts and wedgings, the feet can be brought up in dorsiflexion and still be maintained in the normal position in the midline. In this way the achilles tendon is more thoroughly stretched. The photographs illustrating Thomson's method show the feet in an undesirable amount of valgus. The object of treatment is to produce as nearly normal feet as possible and not severe flatfeet. It is claimed that as the child extends one knee in kicking it will flex the other and thereby stretch the achilles tendon. My patients learned to kick both feet at the same time and avoided this stretching. The 5 children were treated in the hospital where they could be observed, and the nurses thought that they were more "fussy" and not as comfortable as the children treated with plaster casts. Because of inability to correct all the forefoot adduction, and to dorsiflex the feet in the position desired, all of these children were finally put back in plaster casts to finish the treatment. Even though plaster requires more material, time, labor and trained assistants, the better results obtained in my hands justified the extra effort.]

A series of 15 young children with congenital clubfeet is reported on by Davis.[18] He concludes the article, which contributes nothing new, with the statement, "Treatment must constantly be altered to fit the progress made by each individual, and this certainly cannot be done if the patient is not seen frequently by his doctor." In discussing operations on the bones for the older children he says: "It is a safe rule not to attempt interference of this kind until the child is at least eleven years old. It must be borne in mind that osteotomy sites will not unite without adequate bone." [ED. NOTE: I agree with the author in advising the postponement of operations on the bones until the child is older. However, I wonder if any one has ever seen a nonunion occur after an osteotomy at an early age. Forcible manipulations and operations on the bones at an early age usually cause an undesirable amount of stiffness and fusion, both fibrous and bony.]

Torpin [19] reports the case of a newborn infant with prolapsus uteri associated with spina bifida and clubfoot. He gives a review of the literature which leads to the inference that the spina bifida is the primary etiologic factor in the occurrence of the prolapse. It appears that if certain of the sacral nerves are drawn into the spina bifida, there is a partial or complete paralysis of the musculature of the pelvic floor resulting in secondary atrophy.

Coutts [20] recommends nonoperative treatment of clubfoot. He has improved still further the statistics of the Clubfoot Clinic of the New York Orthopaedic Dispensary and Hospital by a modification of the previous technic. The skin of the foot and leg is first painted with tincture of benzoin. This prevents infections of the skin. Elastic adhesive is applied as a series of circular strips. A gap is left

18. Davis, J. B.: Treatment of Congenital Clubfoot in Children, Northwest Med. **41**:238-241 (July) 1942.

19. Torpin, R.: Prolapsus Uteri Associated with Spina Bifida and Club Feet in Newborn Infants, Am. J. Obst. & Gynec. **43**:892-894 (May) 1942.

20. Coutts, M. B.: Adherent Cast in Treatment of Club Foot, J. Bone & Joint Surg. **24**:672-676 (July) 1942.

between the strips at the level of the proposed wedging cuts to avoid wrinkling with the correction. A thin felt strip is affixed by a piece of elastic adhesive to the area where the proximal edge of the wedging cut will impinge. He calls these adherent casts because the elastic adhesive sticks to the skin, and the plaster bandage sticks to the meshes in the outer surface of the elastic adhesive. The plaster cast should be from 2 to 4 mm. in thickness. Older children may use walking irons. The wedging cuts employed leave narrow hinges of plaster at points corresponding to the projection of the axis of the joint which is being corrected. The hinges have proved invaluable in guiding the corrective force along physiologic lines. A retention cast is worn for eight weeks. The mother is taught to manipulate the foot, and a wedge is inserted in the outer border of the heel and sole of the shoe.

Four articles on clubfeet, all of which appeared in 1941, have been translated from the German literature. Müller[21] presents a study of the sex incidence of congenital clubfoot at the Finkenau Gynecologic Clinic in Hamburg during the period 1914 to 1940. In a series of 81,171 births, there were 107 newborn infants with clubfoot, of whom 61 were boys and 46 girls, a ratio of 57 per cent to 43 per cent. Twenty-three of these, including 8 boys and 15 girls (34.8 per cent; 65.2 per cent), did not survive. If the nonviable infants were excluded, the sex incidence was 53 boys to 31 girls or 63.1 per cent to 36.9 per cent. The striking frequency of spina bifida aperta combined with clubfoot in the nonviable infants suggests that the lethal factor may be related to spina bifida aperta. The evident close relation of clubfoot to spinal anomalies should contribute to a clarification of the present problems relating to clubfoot.

The requirements for an efficient night splint are enumerated by Leun.[22] The splint must have a corrective effect on the deformity and prevent return of the foot to a faulty position. It must not require too much intelligence on the part of the parents to apply it. Application should be so simple as to be fool-proof. The splint should be light, so as to hinder as little as possible the movements of the foot. It must be cheap. The author describes a duralumin splint developed from Gocht's splint. An illustration shows the construction and mode of application. Its corrective action and the mode of application are described.

The surgical correction of the talipes equinus factor in congenital clubfoot after nonsurgical preliminary treatment is discussed by Debrunner.[23] In some cases the talipes equinus factor, manifested by contracture of the achilles tendon and by permanent plantar flexion of the tarsus and the ankle, resists the nonsurgical treatment generally used for early treatment of congenital clubfoot. This failure is due chiefly to the marked contracture of a strong tendon and to the shortness of the lever. In such cases after successful correction of outward tilting and adduction, special treatment is required for the talipes equinus factor.

Various procedures have been devised, such as lengthening of the achilles tendon and Schede's procedure. Debrunner has used open tenotomy, which does away with the main obstacle. However, this will not always suffice to give room for adjustment of the talus. For this reason he now directs attention to overcoming the ligamentous obstacles in the vicinity of the capsule of the ankle joint, as earlier advocated by Vulpius. This operation, after preliminary nonsurgical treatment in severe cases, will practically always prevent recurrence and achieve the best possible correction of the deformity. Careful postoperative treatment is of course

21. Müller, R.: Sex Ratio of Incidence in Congenital Clubfoot, Ztschr. f. Orthop. **72**:237-250, 1941.

22. Leun, W.: Night Splints in Therapy of Clubfoot, Ztschr. f. Orthop. **72**:250-253, 1941.

23. Debrunner, H.: Surgical Correction of Talipes Equinus Factor in Congenital Clubfoot After Nonsurgical Preliminary Therapy, Zentralbl. f. Chir. **68**:1613-1616 (Aug. 23) 1941.

necessary with special attention to proper splints, shoes, exercises, etc. The plaster cast can be removed after three weeks.

Thomasen,[24] in discussing the causes of congenital clubfoot, says it appears to be but slightly probable that external conditions during pregnancy play any role in its development. The pathogenesis of the deformity has not been fully established, but it seems to involve an inhibitory malformation. He refers to the work of Wisbrun (1932), who sets forth some new points of view concerning the nature of the deformity and its treatment, saying that it involves a supination of the foot. Thomasen has studied the mechanism and anatomy of the deformity and agrees that the congenital clubfoot is a supination deformity with an equinus contracture in the ankle joint. The supination deformity can be analyzed as consisting in: (1) a supination rotation of the foot; (2) an inversion, or inward rotation of the foot as a whole in relation to the talus, and (3) an inflection, or medial and plantar flexion of the foot at the level of the joint of Chopart.

The essential feature of the supination deformity is the supination position of the calcaneus in relation to the talus. The calcaneus is turned round its longitudinal axis in the direction of supination, but at the same time it also turns round a vertical axis, so that its anterior end swings medially and plantarly in relation to the talus (inversion). Owing to its intimate ligamentous connection with the calcaneus, the navicular bone follows it in relation to the talus, so that it turns medially on the head of the talus and the foot is flexed medially in the joint of Chopart (inflection).

The inversion of the calcaneus in relation to the talus brings about the inversion of the foot as a whole in relation to the ankle joint and the leg, so that the foot points medially as long as the supination deformity remains. The amount of inversion of the foot affords a serviceable expression for the degree of the supination deformity.

Dorsoplantar roentgenography of the foot gives an impression of the supination of the tarsus and especially of the inversion of the calcaneus in relation to the talus. The calcaneus and the talus form an angle which in the normal foot of a child is about 35 degrees. In a foot with a valgus deformity this angle is greater than 35 degrees and may be as great as 70 to 80 degrees, while in a supination deformity it is less than 35 degrees, and may even be zero. In comparison with the clinical observations, the diminution of the calcaneus-talus angle corresponds to the clinical inversion.

These features can be demonstrated by pathologic anatomic studies, and it is appropriate here to call attention to "De anatomia pathologica pedis equini et vari," a Danish work by Johan Christian Weis, who in 1842 emphasized these very features as essential in the nature of the congenital clubfoot.

Thomasen gives a technic for manual redressment by which the supination deformity may be corrected as well as the equinus. Finally, description is given of an "ideal" retaining bandage. In some cases it has been difficult to preserve the correction of the equinus contracture, so that lengthening of the achilles tendon had to be performed subsequently.

The progress and outcome of the treatment have been controlled clinically and roentgenographically. A "satisfactory correction" is considered to have been achieved when the form and position of the foot are normal and roentgenograms show a mutual position of the bones corresponding to that in a normal foot.

---

24. Thomasen, E.: The Congenital Clubfoot: The Mechanics of the Deformity and Its Primary Treatment, Acta orthop. Scandinav. **12**:33-100, 1941.

II. CONGENITAL DISLOCATION OF THE HIP

PREPARED BY DR. A. BRUCE GILL, PHILADELPHIA

There has been little in the literature during the year 1942 on congenital dislocation of the hip. The most important contributions are two articles on dysplasia of the acetabulum.

Goodwin and Cameron [25] make a brief review of the literature and discuss the incidence and the signs and symptoms of the condition. They advise reduction by gentle manipulation for children up to the age of 8 years but do open reduction of any dislocation believed to be either irreducible or incapable of being permanently reduced without operation. They employ the shelf operation for reconstruction of the acetabulum and point out, properly, that the shelf should be placed low and should constitute an extension of the roof of the acetabulum over the head of the femur.

Krida [26] discusses the incidence, the pathology and the symptomatology of congenital dislocation of the hip. He states that this condition can be cured only in infancy or early childhood. After this period of life has passed there is no treatment that can restore the hip to normal condition. The treatment is by manipulation if possible. If manipulation is not possible, he advises open reduction. If there is considerable anteversion of the neck of the femur he advises a supracondylar osteoclasis after the hip has been reduced and has remained fixed in plaster for three months. He believes that the compensatory correction of anteversion by means of osteoclasis is necessary to prevent redislocation of the hip and that anteversion does not correct itself spontaneously.

Colonna [27] makes a late follow-up report on the operation which he first described in 1932. Preliminary traction is employed to pull the head of the femur downward to the site of the primary acetabulum. The hip is exposed at the time of operation by cutting the long head of the rectus femoris muscle and reflecting the great trochanter upward and backward. The isthmus of the capsule is identified and is cut transversely. The proximal portion of the capsule is then sutured together to cover the head of the femur. An excavation is reamed out of the pelvis to hold the head of the femur, which is now completely covered with the capsule. The trochanter is replaced and the wound is closed. The extremity is fixed in a plaster cast to maintain 20 degrees abduction of the hip. Continued traction is employed within the cast. Four weeks later active and passive movements of the hip are begun. In this paper the author reports the end results for 6 patients examined from seven to twelve years after operation. Function in their hips is excellent. He advocates this method of arthroplasty for two types of patients: those under 3 years of age in whom reduction cannot be maintained after closed manipulation, and those between 3 and 10 years of age, for whom it is the method of choice.

Elsner [28] reports in detail 2 cases of congenital dysplasia of the hip with spontaneous healing. He emphasizes the fact that the primary lesion in congenital

25. Goodwin, F. C., and Cameron, D. M.: Congenital Dislocation of the Hip (Its Incidence in New Mexico), Southwestern Med. **26**:105-108 (April) 1942.

26. Krida, A.: Congenital Dislocation of the Hip: General Considerations and System of Curative Treatment, S. Clin. North America **22**:553-563 (April) 1942.

27. Colonna, P. C.: Arthroplasty for Congenital Dislocation of the Hip: Late Follow-Up Report, J. Bone & Joint Surg. **24**:812-826 (Oct.) 1942.

28. Elsner, W.: Spontaneous Healing of Congenital Dysplasia of the Hip, Zentralbl. f. Chir. **68**:1983-1988 (Oct. 18) 1941.

dislocation of the hip is dysplasia of the acetabulum and the head of the femur. This must be kept in mind when processes of development are being considered. It is the congenital dysplasia which permits luxation of varying degree or goes on to spontaneous healing. Spontaneous healing may occur in the second and the third year. Spontaneous healing of actual dislocations is rare, about 34 cases having been reported in the literature. In the first case reported by Elsner spontaneous healing took place in spite of poor conditions with abrupt declivity of the femoral neck. Care is needed in evaluating the dislocation tendency of a dysplasia, since this cannot always be predicted. In the second case, in which the deformity was bilateral, spontaneous healing occurred on one side, that with initially the apparently worse prognosis. Nagura has observed numerous cases of spontaneous healing of congenital dysplasia and congenital dislocation of the hip, probably because he is a believer in late treatment. It is never justified to postpone treatment in the hope of spontaneous healing, since reduction is much easier in the early stages, even when there is slight dislocation. Elsner prefers to intervene so that the child may recover in time for the normal walking period, even if continence has not yet been attained.

Hart [29] stresses delay or persistent defects in the development of the acetabulum (dysplasia) as the primary cause of subluxation and of dislocation of the hip. This dysplasia has a hereditary background. He cites the work of Faber and other authors to prove that dysplasia without dislocation is more frequent than dysplasia with dislocation and that studies of this familial trait should be based on the dysplasia, as shown in roentgenographic studies of all members of the family, rather than on the dislocation. In other words, dysplasia may occur frequently in successive generations, while frank dislocation may be comparatively rare.

A primary congenital dysplasia of the hip may be severe enough to produce dislocation. On the other hand, it may be so slight that it is corrected during the period of growth and the hip eventually becomes normal. If it is of medium severity, some degree of subluxation results.

If the dysplasia is of minor or very moderate degree, clinical symptoms of fatigue, pain and instability of the hip may never arise. In other patients these symptoms may develop only in adult life. The roentgen examination then reveals the incongruity of the hip joint and evidence of a chronic traumatic osteoarthritis of the hip. The symptoms of these patients are due to a partial instability of the hip (subluxation) and to the presence of the arthritis.

The author rightly insists that dysplasia without dislocation is a distinct clinical and roentgenographic entity and that it should be included in textbooks on congenital dislocation of the hip.

[ED. NOTE.—This is a valuable paper. This defect has not received sufficient attention in genetic studies or in follow-up care after reduction of congenital dislocations. Long-continued observation after reduction is essential to determine whether the primary dysplasia will be corrected by natural processes of growth or will persist and eventually result in subluxation of the hip. If the corrective operation for subluxation is delayed until adult life, it may improve or correct the instability of the hip, but it may not relieve the symptoms which are due to arthritis. It is important, therefore, to restore the congruity of the hip early in life, as soon as subluxation becomes evident, to prevent the secondary pathologic processes from developing.]

29. Hart, V. L.: Primary Genetic Dysplasia of Hip With and Without Classical Dislocation, J. Bone & Joint Surg. **24**:753-771 (Oct.) 1942.

III. DISEASES OF GROWING AND OF ADULT BONE

PREPARED BY DR. R. BEVERLY RANEY, DURHAM, N. C.

Interest in this group of relatively rare and obscure diseases of bone has been manifested during the year by an abdundance of case reports accompanied by brief reviews of the literature. On the other hand, original contributions evincing progress toward an increased understanding of these diseases have been few. The influence of the war is shown in an increased number of articles on caisson disease, the only disease of this group directly related to conditions of military combat.

Caisson Disease.—At high pressure the atmospheric gases, chiefly nitrogen, saturate the blood and are taken up by the fatty tissues. It is now generally agreed that caisson disease is caused by a too rapid liberation of gas into the tissues during decompression. Of orthopedic interest are the late osseous changes which often develop in caisson workers. The affected bones show areas of aseptic necrosis with fibrous invasion, mottled sclerosis and incomplete replacement by new bone. The cause of these changes is believed to be multiple gas embolisms resulting in infarctions. The changes may be located in the diaphysis or beneath the articular surfaces. Herzmark [30] describes a patient who after six years as a caisson worker became disabled by pain in the right shoulder and in both hips. Roentgenographic examination revealed aseptic necrosis in the humeral and femoral heads. Herzmark considers these late osseous changes to be a result of repeated incomplete decompressions. Swain [31] describes destruction of the articular cartilage of the femoral heads in a caisson worker 37 years old who had had pain in the right hip for nine months and who died of a coronary accident. Swain emphasizes the advisability of prophylactic treatment consisting of slow decompression and recompression, and periodic roentgenographic examinations of the bones. He believes that the incidence of caisson disease will increase because of the widespread use of the submarine and of high altitude flying in modern warfare. Bell, Edson and Hornick [32] have demonstrated the roentgenographic changes of aseptic necrosis in 32 workers under conditions of increased atmospheric pressure, none of whom had had symptoms referable to the bones and many of whom had never had "the bends." These investigators believe that the extent of involvement of the various long bones is proportionate to their fat content.

Osteitis Deformans.—Compression of the spinal cord by the thickened vertebrae of osteitis deformans, or Paget's disease, has been described in approximately 20 cases. To this number Gross [33] adds a report on the case of a man 53 years of age whose paraplegia and incontinence were cured by laminectomy at the middle dorsal level.

Orban [34] studied in detail the histologic changes in the sclerotic areas of skulls affected by osteitis deformans. He describes six types of sclerotic bone, which vary distinctly in histologic detail but demonstrate as a group the disordered resorption and new formation of bone characteristic of this obscure disease.

30. Herzmark, M. H.: Bone Changes in Caisson Disease: Report of a Case, Bull. Hosp. Joint Dis. **3**:128-133 (Oct.) 1942.

31. Swain, V. A. J.: Caisson Disease of Bone, with Report of Case, Brit. J. Surg. **29**: 365-370 (April) 1942.

32. Bell, A. L. L.; Edson, G. N., and Hornick, N.: Characteristic Bone and Joint Changes in Compressed-Air Workers: Survey of Symptomless Cases, Radiology **38**:698-707 (June) 1942.

33. Gross, S. W.: Compression of Spinal Cord in Paget's Disease of Vertebrae, Am. J. Surg. **55**:575-577 (March) 1942.

34. Orban, B.: Sclerotic Areas in Skulls Affected with Paget's Disease, Arch. Path. **33**: 607-618 (May) 1942.

The treatment of osteitis deformans remains unsatisfactory. Taylor [35] reports a case in which disabling pain subsided completely after a series of subcutaneous injections of cobra venom. Lyon [36] believes intensive vitamin A therapy an essential part of the treatment and reports the case of a patient who was considered to have Paget's disease with a vitamin A deficiency ascribed to hyperthyroidism. A case of osteitis deformans showing metastatic calcification attributed to treatment with viosterol is reported by Wells and Holley.[37]

Parathyroid Glands, Renal Insufficiency and Bony Changes.—Although its causes remain obscure, primary hyperparathyroidism, characterized by hyperplasia of the parathyroid glands, cystic changes in bones, alterations of the blood chemistry and little or no damage to the kidneys, is a recognized entity. Sherman and Nolan [38] add to the literature a case in which one of the parathyroid glands, of normal size when visualized at operation for removal of a hyperplastic gland, was found at autopsy to have become hyperplastic. In this case the electrocardiogram showed the shortening of the RT interval which has been described previously as occurring in hyperparathyroidism. Chasnoff, Friedfeld and Tunick,[39] reporting on a patient suffering from acromegaly and hyperparathyroidism, discuss the interrelationship of pituitary and parathyroid glands.

Increasing emphasis on impaired renal function as a factor connected with hyperplasia of the parathyroid glands and with cystic bone changes is evident. Jaffe [40] summarizes the differential diagnosis of hyperparathyroidism and states that the cases fall into two groups: those of primary hyperparathyroidism, in which the origin of the disease is in the parathyroid glands, and those of secondary or renal hyperparathyroidism, in which parathyroid hyperplasia is associated with a primary renal insufficiency. He states that the patient with renal hyperparathyroidism is usually under 20 years of age. The history is that of stunted growth and symptoms referable to the kidneys, the phosphorus and the phosphatase content of the serum are elevated, and the calcium content is normal or elevated. The treatment consists of measures to improve renal function.

Andersen and Schlesinger [41] have reported 2 cases of renal hyperparathyroidism in infancy. The presenting clinical picture was that of tetany and acidosis. Postmortem examination revealed severe renal damage, hyperplasia of the parathyroid glands, cystic changes in the bones and metastatic calcification of small arteries.

Cases of renal dwarfism, or renal rickets, have been recorded during the year by Graham and Hutchison,[42] and the subject has been reviewed by Clément.[43]

---

35. Taylor, F. R.: Use of Cobra Venom in Treatment of Osteitis Deformans: Report of a Case, North Carolina M. J. **3**:244-245 (May) 1942.

36. Lyon, E.: Relation of Osteitis Deformans to Hyperthyroidism, Schweiz. med. Wchnschr. **72**:592-596 (May 30) 1942.

37. Wells, H. G., and Holley, S. W.: Metastatic Calcification in Osteitis Deformans (Paget's Disease of Bone), Arch. Path. **34**:435-442 (Aug.) 1942.

38. Sherman, C. F., and Nolan, D. E.: Hyperparathyroidism, Am. J. Roentgenol. **47**: 882-888 (June) 1942.

39. Chasnoff, J.; Friedfeld, L., and Tunick, A. M.: Hyperparathyroidism in Patient with Acromegaly, Ann. Int. Med. **16**:162-175 (Jan.) 1942; correction, ibid. **16**:369 (Feb.) 1942.

40. Jaffe, H. L.: Primary and Secondary (Renal) Hyperparathyroidism, S. Clin. North America **22**:621-639 (April) 1942.

41. Andersen, D. H., and Schlesinger, E. R.: Renal Hyperparathyroidism with Calcification of Arteries in Infancy, Am. J. Dis. Child. **63**:102-125 (Jan.) 1942.

42. Graham, S., and Hutchison, J. H.: Familial Renal Dwarfism, Arch. Dis. Childhood **16**:253-256 (Dec.) 1941.

43. Clément, R.: Renal Dwarfism and Renal Rickets, Presse méd. **49**:477-483 (April 30-May 3) 1941.

The outstanding manifestations are grave renal lesions and retarded growth. The data in cases of this type are often incomplete, and the exact relationship of renal dwarfism to renal hyperparathyroidism remains obscure.

Pituitary Gland, Thyroid Gland and Growth of Bone.—In one of the few experimental studies in this branch of orthopedics reported during the year, Becks and his associates [44] observed the effects of thyroxin and anterior pituitary extract on bone growth in rats. In addition to normal animals, the subjects included rats from which the thyroid and parathyroid glands, the pituitary gland or all of these glands had previously been extirpated. The authors conclude that thyroxin and anterior pituitary extract have a synergistic action in promoting growth of bone, and that of the two anterior pituitary extract is the more important.

Fibrous Dysplasias of Bone with Extraskeletal Changes.—In 1937 Albright and his associates described 5 patients who showed fibrocystic bone changes and areas of brown pigmentation of the skin. Precocious puberty was evident in the female but not in the male patients. The age of onset was early, at or before 10 years, and the first symptom in most cases was a pathologic fracture. The blood chemistry was normal. The name of "Albright's syndrome" has been applied to this condition. In a recent article, Gorham and his associates [45] state that 49 instances of the syndrome have been reported; to these they add 2 other cases. The cause of this syndrome has not been determined. Albright suggested that it might be a neurologic disturbance or an embryologic defect. White [46] reports 1 similar case which he believes to be the result of a congenital abnormality in the maturation of fibrous tissue.

In 1938 Lichtenstein reported 8 cases of a similar or possibly identical disease, which he termed "polyostotic fibrous dysplasia." Lichtenstein and Jaffe [47] have recently described 15 additional cases. Small rarefied lesions appear in roentgenograms of the involved bone or bones, pathologic fracture may occur, areas of pigmentation of the skin are present and precocious puberty takes place in the female. The authors ascribe the syndrome to defective development of the bone-forming mesenchyme.

Osteomalacia.—Of interest in demonstrating a pathogenesis for one type of osteomalacia is a case reported by Miyakawa and Stearns.[48] The patient, a victim of long-continued steatorrhea, manifested a severe and rapidly progressing osteoporosis accompanied with pathologic fractures. The authors suggest that in this case the chronic steatorrhea impaired the absorption of minerals and of fat-soluble vitamins. After treatment with a low fat diet supplemented with vitamin D, bile salts, pancreatin and calcium lactate, the phosphatase content of

44. Becks, H.; Ray, R. D.; Simpson, M. E., and Evans, H. M.: Effect of Thyroxin and Anterior Pituitary Growth Hormone on Endochondral Ossification; Species Used: Rat, Arch. Path. **34**:334-357 (Aug.) 1942.

45. Gorham, L. W., and others: Albright's Syndrome: Group of Cases Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Gonadal Dysfunction, Clinics **1**: 358-385 (Aug.) 1942.

46. White, E. H.: Polyostotic Fibrous Dysplasia, Surgery **11**:607-623 (April) 1942.

47. Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone: Condition Affecting One, Several or Many Bones, Graver Cases of Which May Present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism or Still Other Extraskeletal Abnormalities, Arch. Path. **33**:777-816 (June) 1942.

48. Miyakawa, G., and Stearns, G.: Severe Osteoporosis (or Osteomalacia) Associated with Long-Continued Low-Grade Steatorrhoea, J. Bone & Joint Surg. **24**:429-437 (April) 1942.

the patient's blood dropped to a normal level and her bones regained normal density.

Fragilitas Ossium.—Rudolph [49] reports a study of the different types of fragilitas ossium, or brittle bones, and their hereditary basis. He describes 4 cases of congenital osteogenesis imperfecta characterized by multiple fractures at birth and severe deformities, 5 cases of osteopsathyrosis idiopathica characterized by spontaneous fractures after birth and 3 cases showing mixed characteristics. From the genetic observations he concludes that a single pathogenesis may underlie both congenital osteogenesis imperfecta and idiopathic osteopsathyrosis.

In a study of recurrent fractures, Evans [50] points out that many of the patients are children whose bluish scleras and lax ligaments suggest a constitutional background like that of fragilitas ossium.

Osteopetrosis and Osteopoikilosis.—Anthony and Pollack [51] report a case of osteopetrosis, or marble bones, in a Negro girl in whom blindness developed gradually during childhood because of constriction of the optic nerves by narrowed optic foramens; in the same patient a pathologic fracture of the femur occurred at the age of 9 years. Kellogg and Linsman [52] and McLean [53] have reported 3 additional cases of osteopoikilosis, or osteopathia condensans disseminata.

Dyschondroplasia.—During the year, about 42 cases have been added to the literature. Among these is a group of 36 patients with hereditary deforming dyschondroplasia described by B. T. Vanzant and F. R. Vanzant.[54] These patients were in five generations of a family numbering 78 members, some of whom had intermarried. The disease was transmitted as a mendelian dominant.

Morquio's Disease.—Marcos and Pieroni [55] report 3 instances, in sisters, of this obscure infantile chondro-osteodystrophy, which has received considerable attention in pediatric journals but little in the orthopedic literature. The disease is characterized roentgenographically by widespread anomalies of epiphyseal ossification and clinically by the gradual development of multiple and severe deformities. The cause has not been established. Marcos and Pieroni state that 45 cases have been reported.

Calcinosis.—Ghormley [56] reports an interesting and unusual case of multiple large cystic and calcareous masses occurring in bursal areas of the extremities. Two siblings of the patient were similarly affected. Studies of the calcium balance gave negative results. The cause of this condition, which appears to be a form of calcinosis circumscripta, has not been established.

---

49. Rudolph, S.: Identity of Osteogenesis Imperfecta Congenita and Osteopsathyrosis Idiopathica, Monatschr. f. Kinderh. **88**:200-221, 1941.

50. Evans, W. A., Jr.: Recurrent Fracture, Surg., Gynec. & Obst. **74**:204-219 (Feb.) 1942.

51. Anthony, B. W., and Pollack, H. M.: Marble Bones with Pathologic Fractures and Bilateral Optic Atrophy in Negro Child, Radiology **38**:355-359 (March) 1942.

52. Kellogg, D. S., and Linsman, J. F.: Osteosclerosis Fragilis, Osteopathia Condensans Disseminata: Two Case Reports, Southwestern Med. **26**:44-47 (Feb.) 1942.

53. McLean, E. H.: Osteopoikilosis: Disseminated Osteosclerosis, Northwest Med. **41**:92-93 (March) 1942.

54. Vanzant, B. T., and Vanzant F. R.: Hereditary Deforming Chondrodysplasia, J. A. M. A. **119**:786-790 (July 4) 1942.

55. Marcos, J. R., and Pieroni, L. A.: Dyschondroplasia (Morquio's Disease) with Report of Three Cases in Same Family, Arch. de pediat. d. Uruguay **12**:625-648 (Oct.) 1941.

56. Ghormley, R. K.: Multiple Calcified Bursae and Calcified Cysts in Soft Tissues, Tr. West. S. A. (1941) **51**:292-308, 1942.

IV. CHRONIC ARTHRITIS

PREPARED BY DR. LORING T. SWAIM, BOSTON

General.—Knowledge of rheumatic disease has increased, and the investigators are constantly following the new leads which present themselves. However, one is confronted with a complex problem which requires an open mind and a critical attitude toward new and untested methods of treatment. As Pemberton and Scull [57] have pointed out, arthritis is the resultant of many factors and represents the cumulative effects of a "total war," and recovery requires treatment which constitutes "total support." This "total support" means rest and nutrition because of the malfunctioning of many systems, chief among which is the gastrointestinal tract. The diet must be carefully chosen so as not to overload the atonic bowel and to furnish adequate amounts of vitamins, supply the deficiency of protein, correct the anemia and maintain the water balance. There is no routine treatment; all means must be used, including physical therapy.[58] Freyberg [59] makes the following statement:

> Treatment must be individualized for each patient and should be based upon two main objectives; (1) to establish optimal general health and comfort and to prevent as much as possible deformities and crippling, and (2) to arrest the inflammatory process if possible. Among the general measures, rest, physical therapy, exercises of affected joints, relief of discomfort, adequate nutritious diet, orthopedic measures and correction of associated disorders, such as anemia, are of definite value.

An excellent summary [60] has been published in *The Journal of the American Medical Association* under the auspices of the American Rheumatism Association. This primer gives the present American conception of arthritis.

Gold Salts.—The interest in gold salts as a means of treating rheumatoid arthritis is increasing. The problem is still to find an effective soluble salt which is not toxic. Cooperative research is in progress.[61] Reports of the satisfactory results obtained with rheumatoid arthritis increase as knowledge of the action, dosage and physiologic handling of the gold compounds increases. Since the dangers are better understood they can be more easily avoided.[62]

Dawson, Boots and Tyson [63] state: "Chrysotherapy offers greater promise than any other form of therapy in the treatment of rheumatoid arthritis. However, the danger of gold salts cannot be too strongly emphasized. In spite of its obvious disadvantages, the continuation of this type of therapy in the hands

57. Pemberton, R., and Scull, C. W.: Generic and Specific Influences of Nutrition in Total Support of Arthritics, Ann. Rheumat. Dis. **3**:42-56 (May) 1942.

58. Solomon, W. M.: Physical Therapy in Arthritis, Arch. Phys. Therapy **23**:457-466 (Aug.) 1942. Pemberton, R.: Refinements in Treatment of Arthritis Especially in Relation to Physical Therapy, ibid. **23**:581-587 (Oct.) 1942. Treusch, J. V., and Krusen, F. H.: Follow-Up Study of Physical Therapy Applied at Home for Arthritis, Proc. Staff Meet., Mayo Clin. **17**:524-528 (Oct. 7) 1942.

59. Freyberg, R. H.: Recent Trends in the Treatment of Rheumatoid Arthritis, Ohio State M. J. **38**:813-820 (Sept.) 1942.

60. Jordan, E. P., and others: Primer on Arthritis, Prepared by Committee of the American Rheumatism Association, J. A. M. A. **119**:1089-1104 (Aug. 1) 1942.

61. Sabin, A. B.: New Gold Salt for Treatment of Rheumatoid Arthritis: Experimental and Clinical Studies, Proc. Staff Meet., Mayo Clin. **17**:542-544 (Oct. 21) 1942. Baker, D. M.: Gold Injections in Treatment of Arthritis, M. Press **206**:419-421 (Dec. 3) 1941. Cecil, R. L.; Kammerer, W., and dePrume, F. J.: Gold Salts in Treatment of Rheumatoid Arthritis: Study of Two Hundred and Forty-Five Cases, Ann. Int. Med. **16**:811-827 (May) 1942.

62. Freyberg, R. H.; Block, W. D., and Wells, G. S.: Gold Therapy for Rheumatoid Arthritis: Considerations Based upon Studies of Metabolism of Gold, Clinics **1**:537-670 (Oct.) 1942.

63. Dawson, M. H.; Boots, R. H., and Tyson, T. L.: Gold Salts in Treatment of Rheumatoid Arthritis, Tr. A. Am. Physicians **56**:330-338, 1941.

of careful clinicians is both desirable and justifiable." Nothing, however, gives the striking improvement associated with pregnancy or with jaundice. Without repeated laboratory studies of the blood and urine, it is dangerous to give a gold compound.[64] Judicious administration of small doses of a gold salt is strongly recommended, since its excretion is slow and danger lies in too rapid accumulation of gold in the body.[65] Even when caution is exercised gold therapy remains extremely dangerous, and the delayed toxic effects may be fatal.[66]

[ED. NOTE.—There is mention in the German literature of a copper preparation which is said to be superior to gold for chronic rheumatoid arthritis.[67]]

Gout.—Numerous papers [68] have been written about gout, because apparently after having had a period of neglect, the disease is being found again and studied more carefully, with better understanding. Hereditary factors are important and are often overlooked.[68a] It is important to investigate relatives of gouty patients for hyperuricemia. In one family, the father and all three sons had gout. Gout is rare in Negroes. In 2 cases reported by Cohen [68b] the patients were found to have several white ancestors. Treatment during the acute stage consists of rest, medication with colchicine, administration of liberal amounts of fluids, application of epsom salt packs and use of a diet low in protein and fat.[68f] During the intercritical periods small doses of colchicine are given and a purine-free diet, low in fat and high in carbohydrates, is prescribed. In Central Europe the war has shown that a meatless diet is of value.[68e]

Fibrositis.—The term fibrositis has long been used to designate a disease characterized by pain and nodules in the muscles and especially by changes in the fibrinous structure. In this country fibrositis has not been designated as such, or possibly has not been recognized.

Moynahan and Nicholson [69] report 5 typical cases, with a discussion of the incidence, etiology, pathology, symptomatology, differential diagnosis and treatment. They used infiltration with procaine hydrochloride and achieved good results. Schmidt,[70] on the basis of a study of the miners employed by the Butterley Company, says that fibrositis is the most common rheumatic disease in English coal miners. Because of it not less than 2,465 shifts and 15,958 tons of coal

64. Rosenberg, E. F.: Present Status of Gold Therapy for Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **17**:264-271 (April 29) 1942.

65. Freyberg, R. H.: Gold Salts in the Treatment of Chronic Arthritis: Metabolic and Clinical Studies, Proc. Staff Meet., Mayo Clin. **17**:534-541 (Oct. 21) 1942. Robinson, R. H.: Gold Therapy in Rheumatoid Arthritis, Canad. M. A. J. **47**:158-161 (Aug.) 1942. Preston, W. S.; Block, W. D., and Freyberg, R. H.: Chemotherapy of Chronic Progressive Arthritis of Mice: Role of Sulfur in Gold-Containing Compound, Proc. Soc. Exper. Biol. & Med. **50**:253-256 (June) 1942. Freyberg, Block and Wells.[62]

66. Snyder, R. G.; Traeger, C. H., and Squires, W. H.: Toxic Reactions and Death Following Gold Therapy in Chronic Arthritis, Indust. Med. **11**:425-429 (Sept.) 1942.

67. Fenz, E.: Ebesal (Copper Preparation) in Chronic and Subacute Arthritis, München. med. Wchnschr. **88**:1101-1105 (Oct. 10) 1941.

68. (*a*) Smyth, C. J., and Freyberg, R. H.: A Study of the Hereditary Nature of Gout: A Report of Two Families, Ann. Int. Med. **16**:46-56 (Jan.) 1942. (*b*) Cohen, A.: Gout and the Negro, South. Med. & Surg. **103**:654-655 (Dec.) 1941. (*c*) Cohen, A.: Gout: The Modern Disease, ibid. **98**: 637-642 (Dec.) 1936. (*d*) McEwen, C.: The Use of High Fat and High Purine Diets in the Diagnosis of Gout, J. Mt. Sinai Hosp. **8**:854-862 (Jan.-Feb.) 1942. (*e*) Symposium on Gout and Gouty Articular Lesions, Med. Klin. **37**:981 (Sept. 26); 1008 (Oct. 3); 1027 (Oct. 10) 1941. (*f*) Talbott, J. H.: The Treatment of Gout, Bull. New York Acad. Med. **19**:318-328 (May) 1942.

69. Moynahan, E. J., and Nicholson, E. S.: Value of Procaine Infiltration in Diagnosis and Treatment of Fibrositis, Brit. M. J. **1**:65-68 (Jan. 17) 1942.

70. Schmidt, L.: Rheumatism and Industry: Miners' Share, Brit. J. Phys. Med. **5**:145-148 (Sept.-Oct.) 1942.

have been lost a year in the mines of the Butterley Company alone. On the basis of these figures Schmidt estimates that in Great Britain 1,304,029 tons of coal per year is lost. To the loss of production must be added other economic damages, such as lost wages and costs of medical treatment, which are estimated at 6,000,000 pounds. He quotes Buckley, who studied 5,292 rheumatic patients from an industrial area. One thousand five hundred and eighty-three were miners and 50 per cent of them had fibrositis. Schmidt says that drafts and cold are the chief etiologic factors.

Beeson and Scott [71] report 125 cases of a form of myalgia of the neck which may develop into general fibrositis. It occurred in epidemics, and in 40.8 per cent of the cases there were associated infections of the upper respiratory tract. The trapezius, deltoid, rhomboid and scapular muscles were affected. Fifty-five per cent of the patients complained of tenderness. Nodules in the affected muscles, pain on motion and general discomfort were also frequently associated with the disease. Experiments on human subjects indicated that it could be transmitted by blood but not by nasal secretions. Like many of the more familiar communicable diseases, it is a mild, self-limited infection.

Steinberg [72] used vitamin E (tocopherols) both orally and parenterally, in the treatment of primary fibrositis. Because both primary fibrositis and nutritional muscular dystrophy respond to such treatment, he concludes that primary fibrositis is a nutritional disease associated with deprivation of vitamin E. He uses 300 mg. of mixed tocopherols daily the first week, 150 mg. by mouth daily for the next two weeks and 100 mg. daily for maintenance. He believes, however, that 1 mg. of tocopherols per kilogram of body weight per day would be sufficient for the average person.

Ingham [73] reports 12 cases of primary fibrositis treated with vitamin E. His results substantiate Steinberg's conclusion that vitamin E is of value in the treatment of fibrositis. Relief was obtained in three to four weeks with either wheat germ oil in daily doses of 2 to 8 cc. or synthetic vitamin E (alpha tocopherol acetate) in doses of 3 mg. three times a day.

Palindromic Rheumatism.—In June 1941 Hench [74] in his presidential address before the meeting of the American Rheumatism Association called attention to a "new" oft recurring disease of joints apparently producing no articular residues. He called this "palindromic rheumatism." It is characterized by multiple afebrile attacks of arthritis, periarthritis and para-arthritis, with pain, swelling, redness and disability. It occurs in one to many joints, small or large, and is slightly more prevalent among females. The attack appears suddenly and develops rapidly and lasts from a few hours to several days. In spite of the presence of an acute inflammatory polymorphonuclear exudate, there are no constitutional reactions or abnormalities. Laboratory tests reveal no significant residues after numerous attacks. Hench's cases resemble Solis-Cohen's 27 cases of "angioneural arthrosis," which he described in 1911 and 1913, and Kahlmeter's 45 cases of "allergic

71. Beeson, P., and Scott, T. F. M.: Clinical Epidemiological and Experimental Observations on Acute Myalgia of Neck and Shoulder: Its Possible Relation to Certain Cases of Generalized Fibrositis, Proc. Roy. Soc. Med. **35**:733-740 (Sept.) 1942.

72. Steinberg, C. L.: The Tocopherols (Vitamin E) in the Treatment of Primary Fibrositis, J. Bone & Joint Surg. **24**:411-423 (April) 1942.

73. Ingham, D. W.: Treatment of Fibrositis with Vitamin E, M. Ann. District of Columbia **10**:470-471 (Dec.) 1941.

74. Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism: A "New," Oft-Recurring Disease of Joints (Arthritis, Peri-Arthritis, Para-Arthritis) Apparently Producing No Articular Residues: Report of Thirty-Four Cases (Its Relationship to "Angioneural Arthrosis," "Allergic Rheumatism" and Rheumatoid Arthritis), Proc. Staff Meet., Mayo Clin. **16**:808-815 (Dec. 17) 1941.

rheumatism," reported in 1939. Hench states that there may be 10 to 250 attacks a year, lasting from two to seven days. In 80 per cent of the cases the usual duration of the attacks was a few hours to three days. In 70 per cent the longest attacks lasted two to five days. In 90 per cent of the cases the attacks were usually monarticular, but the pain was severe. He states that the similarities among angioneural arthrosis, allergic rheumatism and palindromic rheumatism are more numerous than the differences. The differences are that 30 per cent of Solis-Cohen's patient's were under 12 years of age, whereas none of Hench's were under 13 and most were adults. In 70 per cent of Solis-Cohen's cases the attacks were polyarticular; in Hench's cases they were usually monarticular. Forty per cent of Solis-Cohen's patients had febrile attacks; Hench's did not. Solis-Cohen's patients were ill for many weeks; Hench's usually recovered in four or five days. Allergic reactions were uncommon in Hench's cases, as compared with Kahlmeter's.

Thompson [75] reports 2 cases of palindromic rheumatism, and Mazer [76] reports the case of a 53 year old man who had had recurrent attacks of acute arthritis for thirty years without permanent changes in the joints.

Rhizomelic Spondylitis (Marie-Strümpell).—Freund,[77] in a report on a case of rhizomelic spondylitis, states that in the intervertebral articulations all gradations from fibrous to osseous ankylosis were encountered. There was slight evidence of chronic inflammation. The articular processes of the vertebrae contained coarse fibrous tissue exhibiting chronic inflammatory changes, but not showing any specific appearance of typical rheumatic lesions. No signs of degenerative change were seen within the intervertebral articulation. The disks showed replacement of the cartilage and nucleus pulposus by invading blood vessels and fibrous tissue. The most striking feature is the formation of osseous bridges between two adjacent vertebral bodies. He concludes that ossification of the ligaments was not responsible for the stiffness in the spine in this case, since it was only in the early stages.

Through his roentgenographic studies Oppenheimer [78] found that calcification and ossification of the vertebral ligaments are associated with many different vertebral lesions. He states that they are not typical of any particular disease and should not be confused with arthritis. The ligaments calcify or ossify when their tension and mobility are diminished. Ligaments play no active part in the formation of vertebral osteophytes. He states that complete rigidity of the spine may occur in Marie-Strümpell disease in the absence of ossification of the ligaments. That is, it may be the result rather than the cause of immobility. He believes that calcification or ossification of the vertebral ligaments is a secondary reaction. Its presence often indicates the coexistence of a lesion of the vertebral bone or joints.

Bastow [79] reports 6 cases of ankylosing spondylitis which illustrate the improvement secured even in long-standing disease by use of a plaster shell and complete

75. Thompson, J. L., Jr.: Palindromic Rheumatism: Report of Two Cases, M. Ann. District of Columbia **11**:189 (May) 1942.

76. Mazer, M.: Palindromic Rheumatism, J. A. M. A. **120**:364-365 (Oct. 3) 1942.

77. Freund, E.: Contribution to Pathogenesis of Spondylitis Ankylopoietica, Edinburgh M. J. **49**:91-109 (Feb.) 1942.

78. Oppenheimer, A.: Calcification and Ossification of Vertebral Ligaments (Spondylitis Ossificans Ligamentosa): Roentgen Study of Pathogenesis and Clinical Significance, Radiology **38**:160-173 (Feb.) 1942.

79. Bastow, J.: Some Orthopaedic Procedures Employed in Treatment of Arthritis, Proc. Roy. Soc. Med. **35**:80-84 (Dec.) 1941.

rest in bed. Gradual correction of kyphosis was achieved by adding thin layers of padding under the dorsolumbar junction and removing them from under the head. Deep-breathing exercises, daily physical therapy and use of a Goldthwaite spinal brace were other adjuncts to treatment.

Herrick and Tyson [80] bring out a very important point when they state that ankylosing spondylitis is rare.

> Probably the majority of cases are undiagnosed. Many are wrongly diagnosed and wrongly treated. Perhaps the greatest error is the subjection of many of the victims of this disease to spinal fusion—a measure as futile as it is severe. . . .
>
> The penchant of ankylosing spondylitis for the male in the third to the fifth decade, the great variability of the symptoms, the lack of definition in localizing and describing the pain, its intermittent character, the peculiar attitudes and movements of the patient, the immobility of the thoracic cage, the slight or absent fever, the stiffness of the spine and the abnormal straightening of its lumbar segment, the roentgenographic findings, the elevated sedimentation rate, the occasional involvement of the smaller joints of the extremities and the rarer event of an endocarditis of the rheumatic type, all are important diagnostically. If the physician is alert to this picture, confusion with other pathologic states is unlikely.

The importance of roentgen treatment of rhizomelic spondylitis was emphasized several years ago by Freyberg. Smyth, Freyberg and Lampe [81] state that this form of treatment, if adequately and promptly carried out, has usually been found to give relief in the early stages of the disease.

Scott,[82] of England, has given the lead in this form of treatment. Baker [83] is enthusiastic about a combined treatment. Hyperextension exercises are given, and a special three point brace is applied to maintain correction. Roentgen therapy is given over either the entire spine or the involved area. "Two hundred kilovolts is used in treating areas of about five by fifteen centimeters; 150 roentgen units are given over one or more areas daily for three to five treatments; if necessary the dosage is repeated after three to six weeks." Pain is relieved and correction is easier. The most satisfactory results have been obtained when the disease was in the early stages, but surprisingly good improvement has been noted in some of the patients with definite deformity and advanced calcification.

[Ed. Note.—So far the combination of orthopedic and roentgen therapy has given the best results.]

Blair [84] feels that the pathologic changes in spondylitis "adolescens" are caused primarily by absorption of the cartilage and not by infection and that the beneficial results of the roentgen treatment are brought about by the liberation of sulfur within the body in such a form that it can replenish a sulfur deficiency. He believes that in spondylitis adolescens chondroitin sulfuric acid is absorbed from the cartilage, the ligaments and the bones in and around the sacroiliac joints and spine and that this absorption occurs because of a deficiency of sulfur or the mucoitin or chondroitin sulfuric acids elsewhere in the body. He believes that the iritis associated with spondylitis adolescens is caused by the same metabolic disturbance and possibly may react favorably to the same treatment.

---

80. Herrick, W. W., and Tyson, T. L.: The Medical Aspect of Ankylosing Spondylitis (Marie-Strümpell), Ann. Int. Med. **15**:994-1001 (Dec.) 1941.

81. Smyth, C. J.; Freyberg, R. H., and Lampe, I.: Roentgen Therapy for Rheumatoid Arthritis of the Spine, J. A. M. A. **117**:826-831 (Sept. 6) 1941.

82. Scott, S. G.: Spondylitis Adolescens with Associated Pathological Changes in the Sacro-Iliac Joints, Charterhouse Rheumat. Clin., Orig. Papers **1**:169-203, 1937.

83. Baker, L. D.: Rhizomelic Spondylosis: Orthopaedic and Roentgen Therapy, J. Bone & Joint Surg. **24**:827-830 (Oct.) 1942.

84. Blair, H. C.: Spondylitis Adolescens—Strümpell-Marie Disease: Practical and Theoretical Considerations, Surg., Gynec. & Obst. **74**:663-670 (March) 1942.

Gonorrheal Arthritis.—Kersley and King [85] report a study of the various manifestations of gonorrheal arthritis. They state that the time between infection and the onset of symptoms referable to the joints may be considerable. In 81 per cent of the cases it was longer than ten weeks. The complement fixation test gave positive results in 80 per cent of cases in which the diagnosis was proved and in 60 per cent of those in which it was probable. Positive reactions have been obtained even twenty years after infection. For treatment they recommend doses of sulfonamide compounds sufficient to maintain a concentration of 6 to 10 mg. per hundred cubic centimeters of blood for ten to fourteen days. Fever induced by intravenous injections of typhoid-paratyphoid combined vaccine each containing 10,000,000 or more organisms or by hyperthermy has also proved effective. When hyperthermy is used the temperature is raised to 106 to 107 F. in two to four sessions of 6 to 10 hours each. Ninety per cent of the patients so treated were cured. The combination of sulfanilamide with hyperthermy gives excellent results.

Bauer, Ropes and Short [86] state that the incidence of permanent disability, which was formerly about 25 per cent, should be greatly reduced if treatment with sulfonamide compounds is given early. They prefer sulfathiazole because it is less toxic and use 2 Gm. as the initial dose.

Vitamin D.—The controversy still goes on about vitamin D.[87] Snyder, Squires Forster and Traeger [88] still claim that treatment with vitamin D produces definite functional improvement and that it is safe. Steck [89] reports:

> There is still no adequate explanation of the beneficial results of this method of treating arthritis.
>
> There is no claim that vitamin D is a specific cure for arthritis. Complete freedom from any recurrence of symptoms on cessation of treatment for long periods was found only in a small percentage of cases studied over a period of five years.

However, Slocumb,[90] states that large doses of vitamin D partially controlled the symptoms of infectious arthritis in 7 of 14 cases. Twenty-five courses of daily doses of 52,500 to 386,000 units were given. The periods of treatment lasted from twelve days to fifteen and one-half months. Little objective effect was noted, and beneficial effects were only transitory. There is some risk of renal damage. Gastrointestinal symptoms are indicative of toxicity.

Warkany, Guest and Grabill [91] state: "After abrupt withdrawal of the high daily doses of vitamin D from three to six months elapsed before the concentration of vitamin D in the blood serum fell to a normal level."

---

85. Kersley, G. D., and King, A.: Discussion on Gonococcal Arthritis and "Rheumatism," Proc. Roy. Soc. Med. **35**:653-658 (Aug.) 1942.

86. Bauer, W.; Ropes, M. W., and Short, C. L.: The Treatment of the Infectious Arthritides with Sulfonamide Compounds, M. Clin. North America **26**:1529-1550 (Sept.) 1942.

87. Reynolds, C.: Comparative Therapeutic Value and Toxicity of Various Types of Vitamin D, Journal-Lancet **62**:372-375 (Oct.) 1942.

88. Snyder, R. G.; Squires, W. H.; Forster, J. E., and Traeger, C. H.: Treatment of Two Hundred Cases of Chronic Arthritis with Electrically Activated Vaporized Sterol, Indust. Med. **11**:295-316 (July) 1942.

89. Steck, I. E.: Further Clinical Experience in Treatment of Arthritis with Vitamin D, Ohio State M. J. **38**:440-443 (May) 1942.

90. Slocumb, C. H.: Vitamin D in the Treatment of Infectious Arthritis, Ann. Int. Med. **16**:241-245 (Feb.) 1942.

91. Warkany, J.; Guest, G. M., and Grabill, F. J.: Estimation of Vitamin D in Blood Serum: Vitamin D in Human Serum During and After Periods of Ingestion of Large Doses of Vitamin D, J. Lab. & Clin. Med. **27**:557-565 (Jan.) 1942.

Psoriasis.—Bauer, Bennett and Zeller [92] conclude that "the pathological changes in the joints of patients with arthritis and psoriasis are usually indistinguishable from those of uncomplicated rheumatoid arthritis. . . . Until additional studies have been made, it is our belief that if the term *psoriatic arthritis* is to be used to designate a form of articular disease its use should be restricted to cases in which the arthritis is limited to the terminal phalangeal joints."

Franks and Wallace [93] state that 4 per cent of all cutaneous diseases in America are psoriasis. Arthropathic psoriasis has two forms. The first and more common type follows resistant psoriasis of long duration, while the second type develops simultaneously with the eruption. The rapid improvement in many of the cases of arthritis after the involution of the cutaneous eruption would indicate that the arthritis may be secondary to the disease of the skin. The arthritis was definitely of the atrophic type. Another interesting statement is that the sedimentation rate is usually normal in psoriasis, whereas in arthritis it is rapid. The amount of cholesterol in the blood is high in psoriasis.

Menopausal Arthritis.—Ishmael [94] discusses the treatment of menopausal arthritis. General supportive measures include a diet poor in carbohydrates and rich in vitamins for overweight patients and a normal well balanced diet for those whose weight is normal. Trauma, cold and dampness are to be avoided. Foci of infection are best left intact while active treatment is in progress. Supplementary vitamins are useful when a chemical deficiency is present. Relief of such associated symptoms as gastrointestinal disturbances, emotional upsets and faulty posture may relieve the pain. Specific measures are of two kinds, injections of natural estrogenic substances and injections of diethylstilbestrol. Eighty per cent of the patients whose disease was diagnosed as menopausal arthralgia had satisfactory remissions after the injection of diethylstilbestrol. "In 30 patients, stilbestrol was successfully substituted for estrin. . . . Twenty-three patients (77 per cent) receiving stilbestrol by mouth had clinical remissions as compared with 10 patients (30 per cent) who received estrin that responded by clinical remissions."

Infection.—Very little has been written about infection of late. Bassler [95] states that infections of intestinal origin may be an important factor in the causation of arthritis and suggests a method of biologic and dietetic treatment. The results of gastrointestinal treatment of 205 cases. are presented. About 17 per cent of the patients with digestive diseases causing secondary biotoxic states showed improvement. Among 181 patients with primary biotoxic intestinal conditions, 68.5 per cent showed definite reduction of swelling, with improvement in function of the joints and control of remissions. About 26.5 per cent more were distinctly improved, and for 9.2 per cent the treatment failed.

Preston [96] like Sabin [61] experimented with the arthritis in rats caused by pleuropneumonia-like micro-organisms in an attempt to isolate similar organisms from

92. Bauer, W.; Bennett, G. A., and Zeller, J. W.: Pathology of Joint Lesions in Patients with Psoriasis and Arthritis, Tr. A. Am. Physicians **56**:349-352, 1941.

93. Franks, A. G., and Wallace, J. J.: Arthropathic Psoriasis, Mil. Surgeon **91**:199-205 (Aug.) 1942.

94. Ishmael, W. K.: Menopause Arthralgia, J. Lab. & Clin. Med. **27**:297-303 (Dec.) 1941; Oral Stilbestrol Therapy in Menopause Arthritis, J. A. M. A. **117**:1650 (Nov. 8) 1941.

95. Bassler, A.: Intestine and Chronic Arthritis, Am. J. M. Sc. **203**:698-708 (May) 1942.

96. Preston, W. S.: Arthritis in Rats Caused by Pleuropneumonia-Like Micro-Organisms and Relationship of Similar Organisms to Human Rheumatism, J. Infect. Dis. **70**:180-184 (March-April) 1942.

patients suffering from rheumatoid arthritis. On no occasion was any organism related to the pleuropneumonia group obtained. These negative results agree with those of all other workers reporting similar studies.

Each year more is written about rheumatism connected with brucellosis. Manchester [97] concludes after study of 100 cases that the articular symptoms are not associated with residual deformity or permanent impairment of function. There is no relation between brucellosis and rheumatoid arthritis. Phalen and Prickman [98] report 3 cases of brucellosis spondylitis. The organisms were demonstrated. Fever therapy was effective, although it is not commonly so for other kinds of spondylitis.

Bauer, Ropes and Short [86] report that sulfanilamide and its derivatives are of value in the treatment of arthritis produced by gonorrhea and infections due to streptococci, the meningococcus, the colon bacillus or the pneumococcus. They are of questionable value in undulant fever and lymphogranuloma venereum. Their value for scarlet fever, bacillary dysentery, typhoid, subacute bacterial endocarditis and chronic idiopathic ulcerative colitis is undetermined. They are ineffectual in rheumatic fever, rheumatoid arthritis, tuberculous arthritis and the articular lesions associated with lupus erythematosis disseminatus.

The advent of the sulfonamide compounds represents the greatest advance ever made in the treatment of joint disease. The dramatic alteration in the clinical course of many of the specific infectious arthritides, following the administration of sulfonamide compounds, is adequate evidence that they exert a specific chemotherapeutic effect on certain causative organisms.

Hypertrophic Arthritis of the Hip.—Harmon [99] reports the results of treatment of 79 patients with hypertrophic arthritis of the hip. Two thirds of them were given significant relief from pain and disability by conservative treatment. Harmon feels, however, that operation, preferably arthrodesis or arthroplasty, offers the only lasting relief. Kuhns,[100] on the other hand, says that the symptoms are caused by strain on the muscles and ligaments due to faulty posture. One hundred and fifty-eight patients were given orthopedic treatment designed to correct the strain. Forty-seven, or 29.8 per cent, were relieved of symptoms and 58, or 36.7 per cent, showed great improvement.

Psychologic Aspects.—Halliday [101] found that with 9 of 20 patients with arthritis the onset of the disease was preceded by emotional upsets due to shock, danger, family worries or fear of loss of a love object, with resultant depression, and feelings of frustration. All of them dealt with emotion in a common way. Their feelings were "bottled up." This restriction of feeling and of emotional expression is considered characteristic of the patient with rheumatoid arthritis. Like peptic ulcer, mucous colitis, exophthalmic goiter and asthma, arthritis has phases of ups and downs which can be associated with emotional variations. Halliday states that apparent cures have been produced by pregnancy or by an attack of jaundice. He feels that study of patients who recover "on their own" is important.

(To Be Continued)

97. Manchester, R. C.: Clinical Manifestations and Diagnosis of Chronic Brucellosis, Ann. Int. Med. **16**:950-965 (May) 1942.

98. Phalen, G. S.; Prickman, L. E., and Krusen, F. H.: Brucellosis Spondylitis: Treatment of Physically Induced Hyperpyrexia, J. A. M. A. **118**:859-862 (March 14) 1942.

99. Harmon, P. H.: Pathology and Treatment of Osteoarthritis of Hip, with Special Emphasis on Pin Arthrodesis and Cup Arthroplasty, Pennsylvania M. J. **45**:948-956 (June) 1942.

100. Kuhns, J. G.: Orthopaedic Treatment of Hypertrophic Arthritis of the Hip, J. Bone & Joint Surg. **24**:547-554 (July) 1942.

101. Halliday, J. L.: Psychological Aspects of Rheumatoid Arthritis, Proc. Roy. Soc. Med. **35**:455-457 (May) 1942.